IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

WYETH LLC, WYETH PHARMACEUTICALS LLC, PF PRISM C.V., PFIZER PHARMACEUTICALS LLC, and PFIZER PFE IRELAND PHARMACEUTICALS HOLDING 1 B.V., Plaintiffs, v. ALEMBIC PHARMACEUTICALS, LTD., *et al.* Defendants.	Redacted- Public Version C.A. No. 16-1305-RGA **CONSOLIDATED** [redacted]

BRIEF IN SUPPORT OF SUN'S MOTION TO EXCLUDE THE OPINIONS AND TESTIMONY OF BERNHARDT TROUT, PH.D

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Dated: August 30, 2019

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I. Nature and Stage of the Proceedings

This is a patent infringement action relating to the alleged infringement and invalidity of three patents which purportedly cover Plaintiffs' marketed product containing bosutinib. The parties have completed expert discovery, including expert reports and expert deposition and are preparing for trial in early November. In the Scheduling Order the Court allowed Daubert briefing at the end of expert discovery, and Sun presents this brief in support of its Motion to Exclude the Testimony and Opinions of Bernhardt Trout, Ph.D.

II. Summary of Argument and Statement of Facts

Dr. Trout was engaged by Plaintiffs as one of four (4) individuals to respond to the Opening Invalidity Report of Dr. Craig Lindsley. Specifically, Dr. Trout was asked to respond to Dr. Lindsley's opinion that U.S. Patent No. 7,919,625 ("the '625 patent") is invalid due to anticipation.[1] Dr. Trout opines "a POSA reading Boschelli 2001 would not have understood it to disclose a pharmaceutical composition comprising bosutinib. Thus, my opinion is that Boschelli 2001 does not anticipate the '625 patent." Ex. A (Trout Rpt). ¶ 81. Sun seeks to exclude the opinions and testimony of Dr. Trout because he does not have the requisite knowledge, expertise or understanding of the pertinent art to opine on anticipation of the '625 patent and his opinions are not reliable. More specifically and explained in more detail below:

1. Dr. Trout does not qualify as a Person of Ordinary Skill in the Art ("POSA")

2. Dr. Trout does not understand the process or requirements for animal studies in drug development

3. Dr. Trout is unable to define "pharmaceutically acceptable composition"

[1] Dr. Lindsley offers additional opinions regarding invalidity due to obviousness, lack of written description, enablement and indefiniteness, which are responded to by three other individuals retained by Plaintiffs.

4. Dr. Trout walks away from and contradicts the opinions expressed in his report

5. Dr. Trout "does not have an opinion" on fundamental issues relating to his opinion and conclusions.

III. Legal Standards

The Federal Rules of Evidence "assign to the trial judge the task of ensuring that an expert's testimony both rests on a reliable foundation and is relevant to the task at hand." *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). "Rule 702 has three requirements: (1) the proffered witness must be an expert, *i.e.*, must be qualified; (2) the expert must testify about matters requiring specific, technical or specialized knowledge, *i.e.*, must be reliable; and (3) the expert's testimony must assist the trier of fact, *i.e.*, must be fit." *Meadows v. Anchor Longwall and Rebuild, Inc.*, 306 Fed. App'x. 781, 788 (3d Cir. 2009). The relevant factors to be considered when assessing the reliability of an expert's testimony include: "(1) whether a method consists of a testable hypothesis; (2) whether the method has been subjected to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put." *Oddi v. Ford Motor Co*., 234 F.3d 136, 145 (3d Cir. 2000) (citing *In re Paoli*, 35 F.3d at 742 n.8). However, the list is "nonexclusive" and "each factor need not be applied in every case." *Elcock v. Kmart Corp*., 233 F.3d 734, 741 (3d Cir. 2000). The party offering the expert testimony has the burden of establishing its admissibility by a preponderance of the evidence. *Bourjaily v. United States*, 483 U.S. 171, 175–76 (1987).

The qualification requirement examines whether the witness has "specialized knowledge or training sufficient to qualify him to opine on an issue within his field of expertise." *Pell v. E.I. DuPont De Nemours & Co.*, 231 F.R.D. 186, 192 (D. Del. 2005). In a patent case, an expert testifying on validity or infringement must have at least the expertise of a person of ordinary skill in the art ("POSA"). *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008). Further, an expert's opinions "must be confined to [the expert's] field" of expertise. *Pell*, 231 F.R.D. at 192. "An expert may be generally qualified but may lack qualifications to testify outside his area of expertise." *Calhoun*, 350 F.3d 322 (holding that expert in investigating "aquatic related accident[s]" could testify about "different types of jet skis and their operation," but not whether specific jet ski designs were safe). The more specific the opinions given, the more specific the knowledge required. *Calhoun*, 350 F.3d at 322. Rule 702 "clearly contemplates some degree of regulation of the subjects and theories about which an expert may testify." *Daubert*, 509 U.S. at 589.

IV. Dr. Trout's Opinions and Testimony Regarding Anticipation of the '625 Patent Should be Excluded

A. Dr. Trout is Not Qualified to Opine Regarding Anticipation of the '625 Patent

1. Dr. Trout Does Not Qualify as a Person of Ordinary Skill in the Art

At the outset, Dr. Trout does not qualify as a POSA under either party's definition and most certainly does not qualify as a POSA under Pfizer's definition. In his report, Dr. Trout notes Pfizer's definition of a POSA is:

> someone having the knowledge of (1) an M.D. with several years of experience as an oncologist treating patients with CML; (2) a Ph.D. with several years of experience conducting research on inhibition of tyrosine kinases; and (3) a person with a Ph.D in medicinal chemistry, pharmacology or a related field with several

> years of experience in drug development and formulation. *See* Ex. B (Trout Rpt) ¶25, citing D.I. 91 at 4.

Dr. Trout goes on to note under Pfizer's proposal, a **single** hypothetical individual would have all of the relevant experience. Ex A. (Trout Rpt.) ¶ 27. At his deposition, Dr. Trout admitted he is not POSA under Pfizer's full definition and qualifies his "skill is really focused on the third part of that definition." Ex. B (Trout Tr.) at 21:7-14. Under Sun's definition Dr. Trout similarly fails to meet the standard for a POSA. Sun's proposed definition is a person with:

> a high level of skill, such as an M.D. and several years of experience as an oncologist treating patients with CML, or a Ph.D. and several years of experience conducting research on inhibition of tyrosine kinases. A POSA would have access to and could have collated with individual with pertinent experience, such as medicinal chemistry, biology, pharmacology and/or drug metabolism and pharmacokinetics. A POSA could have a lower degree of formal education is such person had a high degree of expertise. D.I. 91 at 5.

Dr. Trout does not have any experience with the treatment for CML, "outside of just reading the documents in this case." Ex. B. (Trout Tr.) at 12:21-24. Prior to his engagement in this matter, Dr. Trout did not have a specific or detailed understanding of CML, other than knowing Gleevec was a pharmaceutical for the treatment of cancer. *Id*. at 12:25-13:12. Dr. Trout gained his understanding of CML ("to the extent [he has] an understanding") from the '625 patent, the background in Dr. Lindsley's report and some of the exhibits. *Id*. at 14:5-15. Dr. Trout admitted he does not have any experience conducting research specifically on inhibition of tyrosine kinases. *Id*. 15:12-18. Further, his background knowledge on inhibition of tyrosine kinases is general in terms of his study of drug development and inhibition broadly, his understanding is not specific as it relates to the treatment of CML, and his understanding of the role of inhibition of tyrosine kinases in the treatment for CML is based on his general educational background and the documents he reviewed for this matter. *Id*. at 15:19-16:19.

Prior to his engagement in this matter, he did not have any specific understanding of how tyrosine kinases and/or their inhibition were implicated in CML therapy. *Id*. at 16:20-16:25.

In a patent case, an expert testifying on validity or infringement must have at least the expertise of a person of ordinary skill in the art ("POSA"). *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008) In this case, the issues call for consideration of evidence from the perspective of a POSA, and it would be "contradictory to Rule 702 to allow a witness to testify on the issue who is not qualified as a technical expert in that art." *Id*. More specifically, "a witness not qualified in the pertinent art may not testify as an expert as to anticipation, or any of the underlying questions, such as the nature of the claimed invention, what a prior art references discloses, or whether the asserted claims read on the prior art reference." *Id* at 1364. Based on Dr. Trout's background and his testimony, his knowledge and experience do not qualify him as a POSA nor is his expertise appropriately relevant to the pertinent art. Dr. Trout's testimony should be excluded as he is not qualified to opine in relation to the pertinent art and his testimony will not assist the trier of fact.

2. Dr. Trout Fundamentally Does Not Understand the Process or Requirements for Animal Studies in Drug Development

Dr. Trout correctly notes an anticipation defense focuses on "whether a POSA would ***reasonably understand or infer*** that every claim element is disclosed in that reference." Ex. A (Trout Rpt.) ¶31 (emphasis added). However, Dr. Trout's testimony and misunderstanding of the pertinent art makes it clear he is unable to testify as to what a POSA would reasonably understand or infer Boschelli 2001 to disclose. Dr. Trout repeatedly makes incorrect and contradictory assumptions and conclusions, and fails to provide knowledge or opinions relating to the pertinent art.

Dr. Trout criticizes the Boschelli 2001 reference and determines it does not anticipate the '625 patent, because it was not clear to him "the researches took care to synthesize [bosutuinb] for use in animal studies such that the active compound being evaluated would be "pharmaceutically acceptable." Ex. A (Trout Rpt) ¶ 68. He further criticizes Boschelli for not disclosing "that the research took care to procure and use pharmaceutical grade excipients when preparing the composition administered in the reported animal studies." Ex. A (Trout Rpt) ¶ 74. The basis for his opinion is premised on a misreading of the prior art.

A principal reference Dr. Trout relies on for this opinion is Wolff 2003. When specifically confronted with the Wolff reference Dr. Trout admitted Wolff states the use of non-pharmaceutical grade excipients should be based on 1) scientific necessity 2) nonavailability of an acceptable veterinary or human pharmaceutical grade compound and 3) specific review and approval by the IACUC. Ex. B. (Trout Tr.) at 79:14-21. In line with the disclosure of Wolff, Dr. Trout was asked what im Boschelli would lead him to believe there was a scientific necessity to use non-pharmaceutical grade excipients. His response was "I would say it the other way around. There was not a scientific necessity for Boschelli to use pharmaceutical grade compounds." Ex. B. (Trout Tr.) at 79:23-80:7. This is directly contradictory to Wolff, the very reference Dr. Trout relies upon to justify his opinions. Dr. Trout's misinterpretation of Wolff highlights his lack of understanding of the basics relating to animal research.

Dr. Trout's misunderstanding is understandable given he has never conducted animal research. Further, he admitted he did not consult with any of his colleagues who conduct animal research to determine their standard practice. Ex. B. (Trout Tr.) at 81:18-23. Dr. Trout could not state whether a POSA in the art reading Boschelli would believe it was more likely than not that the TWEEN 80 used in Boschelli was pharmaceutical grade, only that there was no indication it

was pharmaceutical grade. Ex. B. (Trout Tr.) at 92:11-93:2. However, based on Wolff and other references, it is clear a POSA would reasonably understand or infer pharmaceutical grade excipients were used, because that is the standard and there was no indication otherwise. *See* Ex. C (Wolff).

Dr. Trout concedes a pharmaceutical composition according to the '625 patent includes compositions formulated for use in animal laboratory research. The Boschelli reference is directed to use of a composition in just such a context. However, Dr. Trout has never done research in laboratory animals and has never read the two governing documents setting out the standards for laboratory research in animals. Ex. B. (Trout Tr.) at 36:25-38:21. Not surprisingly, when confronted with questions regarding the requirements relating to animal research, Dr. Trout repeatedly responded with "I don't have an opinion on that." *See* Ex. B (Trout Tr. 106:18-108:18). Specifically, Dr. Trout was asked whether researchers working with laboratory animals have a duty to ensure the research causes the least possible harm to the animal - Dr. Trout did not have an opinion. Dr. Trout did also did not have an understanding as to the requirements for providing veterinary care to laboratory animals. and did not have an opinion

A POSA reading the Boschelli reference *would* have an understanding of the requirements for conducting laboratory research and it would have informed their understanding and inference of what the Boschelli reference discloses. Dr. Trout is unable to, and indeed does not, provide any reliable opinions on what a POSA would reasonably understand or infer Boschelli to be disclosing about the composition used in the animal studies. As such, Dr. Trout lacks the necessary knowledge and understanding of the pertinent art to testify in this matter and his testimony should be excluded.

B. Dr. Trout Is Unable to Define "Pharmaceutically Acceptable Composition"

The opinion Dr. Trout purports to offer is exceedingly narrow, namely that the Boschelli reference *does not* say the composition it uses to inhibit tumors in mice is a "pharmaceutically acceptable" composition. In fact, Dr. Trout never offers the opinion the composition of Boschelli is *not* pharmaceutically acceptable. *See e.g.* Ex. B (Trout Tr.) at 151:24-152:11. It is not surprising he is unable to reach that conclusion given Dr. Trout was unable to define the criteria one would have to meet to arrive at a "pharmaceutically acceptable" composition.

Dr. Trout offered the opinion Boschelli does not disclose a "pharmaceutically acceptable" composition because (1) the bosutinib was *likely* not pure; and (2) Boschelli does not disclose the excipients used were pharmaceutical grade excipients. Ex. A (Trout Rpt.) ¶¶66-74.[2] However, when asked if the composition of Boschelli would be "pharmaceutically acceptable" if it used pure bosutinib and pharmaceutical grade excipients, Dr. Trout didn't have an opinion. Ex. B (Trout Tr.) at 72:6-75:24. He also didn't form an opinion as to whether the composition could have been reproduced in such a way to make it pharmaceutically acceptable. *Id.* at 157:17-158:3.

Dr. Trout's failure underpins the fact he cannot say what a "pharmaceutically acceptable" composition would be in the context of the '625 patent. Dr. Trout was repeatedly asked what, if anything, would be pharmaceutically acceptable pursuant to the claims. He was unable to do so. *See* Ex. B (Trout Tr.) at 133:4-138:6; 141:11-23; 149:8-150:9. In fact, Dr. Trout does not even know if the *only composition* disclosed in the '625 patent is a pharmaceutically acceptable composition. Ex. B (Trout Tr.) at 165:19-166:7. Dr. Trout's opinions are fundamentally unreliable because he cannot say with any degree of clarity of thought what would constitute a pharmaceutically acceptable composition as that term is used in the '625 patent.

[2] Dr. Trout agrees every excipient used in the Boschelli composition are disclosed in the '625 patent and are generally recognized as safe by FDA.

C. Dr. Trout Repeatedly Walks Away From or Contradicts the Opinions Expressed in His Expert Report

Throughout Dr. Trout's deposition, he contradicted his own expert report by stating he had no opinion on things he explicitly addressed in his report.

In Dr. Trout's report he offers the opinion "the mice [in the Boscelli experiment] did not have CML, and [bosutinib] was not being administered to provide a therapeutic benefit." Ex. A (Trout Rpt) ¶ 67 . Dr. Trout's opinions are further premised on his belief the API used in the experiments were being produced for "screening experiments." *See, e.g., id* at ¶ 69. But at his deposition, Dr. Trout was asked what the objective was of administering the composition to the mice and he answered he didn't have an opinion:

> Q: What was the objective of the Boschelli folks in administering the composition containing bosutinib, Tween 80 and dextrose?"
> …
> A: I didn't speak in my report about the specific objective, so I didn't express an opinion about that."

Ex. B (Trout Tr.) at 145:22-146:5; *see also* 146:19-147:15.

It is fundamentally contradictory to on the one hand express an opinion about the reason a composition was being administered to the mice and simultaneously testify he did not consider why the compositions were being administered to the said same mice. Put differently, Dr. Trout cannot simultaneously offer opinions a composition was "not being administered to provide a therapeutic benefit" and the API was being produced to be used in "screening experiments" and testify he has no opinion about the objective of administering the composition to laboratory animals.

Dr. Trout's failure to offer an opinion on why the composition was being administered further undercuts his related testimony that one would have to have an understanding of the

objectives of administering a compound to understand whether it was a "pharmaceutically acceptable composition."

> Q: Do you have an opinion about what a composition administered to a laboratory animal would have to look like in order for it to be considered pharmaceutically acceptable?
>
> A: … And, again, it would depend on the context, what the study was done for, and I would have to analyze those details."

Ex. B. (Trout Tr.) at 141:11-23.

As previously demonstrated, Dr. Trout cannot define what a "pharmaceutically acceptable composition" is, does not know whether the composition of Boschelli is "pharmaceutically acceptable" and is not qualified to ascertain whether a POSA would reasonably understand or infer it was pharmaceutically acceptable. Furthermore, Dr. Trout failed to undertake the very same analysis he testified was necessary to determine whether the composition was pharmaceutically acceptable. In view of this failure alone, he should not be permitted to testify as to the anticipation of the sole asserted claim of the '625 patent.

D. Dr. Trout "Does not Have an Opinion" on Fundamental Issues Relating to His Opinion

Dr. Trout was either unable or unwilling to offer multiple opinions central to his ultimate conclusions. For example, Dr. Trout testified he does not have an opinion/understanding as to whether or not Claim 1 of the '625 patent requires treating CML with a pharmaceutically acceptable composition. Ex. B (Trout Tr.) at 48:25-49:8. Further, as noted above, in reviewing the '625 patent, Dr. Trout made clear he did not have an opinion as to whether the composition disclosed in the patent described a pharmaceutically acceptable composition. Ex. B (Trout Tr.) at 165:19-166:2.

Further, should Dr. Trout be allowed to testify at trial, Dr. Trout should not be allowed to offer any testimony or opinion regarding any alleged interchangeability of the terms "treating"

and "inhibiting" as used in the '625 patent. Ex. A (Trout Rpt.) ¶37, fn. 1. At Dr. Trout's deposition he stated he did not use those terms interchangeably in formulating his opinions, but was "observing that I think the '625 patent does so." Ex. B (Trout Tr.) at 22:17-23:11. This statement is consistent with his repeated testimony that he does not understand or did not analyze issues central to his opinions and this matter.

V. Conclusion

Based on the foregoing, Sun respectfully requests this Court entering an Order excluding Dr. Trout's opinions and testimony from being presented or relied upon in this matter.

/s/ Nathan R. Hoeschen

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Dated: August 30, 2019

CERTIFICATE OF SERVICE

I, Nathan R. Hoeschen, hereby certify that on August 30, 2019, this document was served on the persons listed below in the manner indicated:

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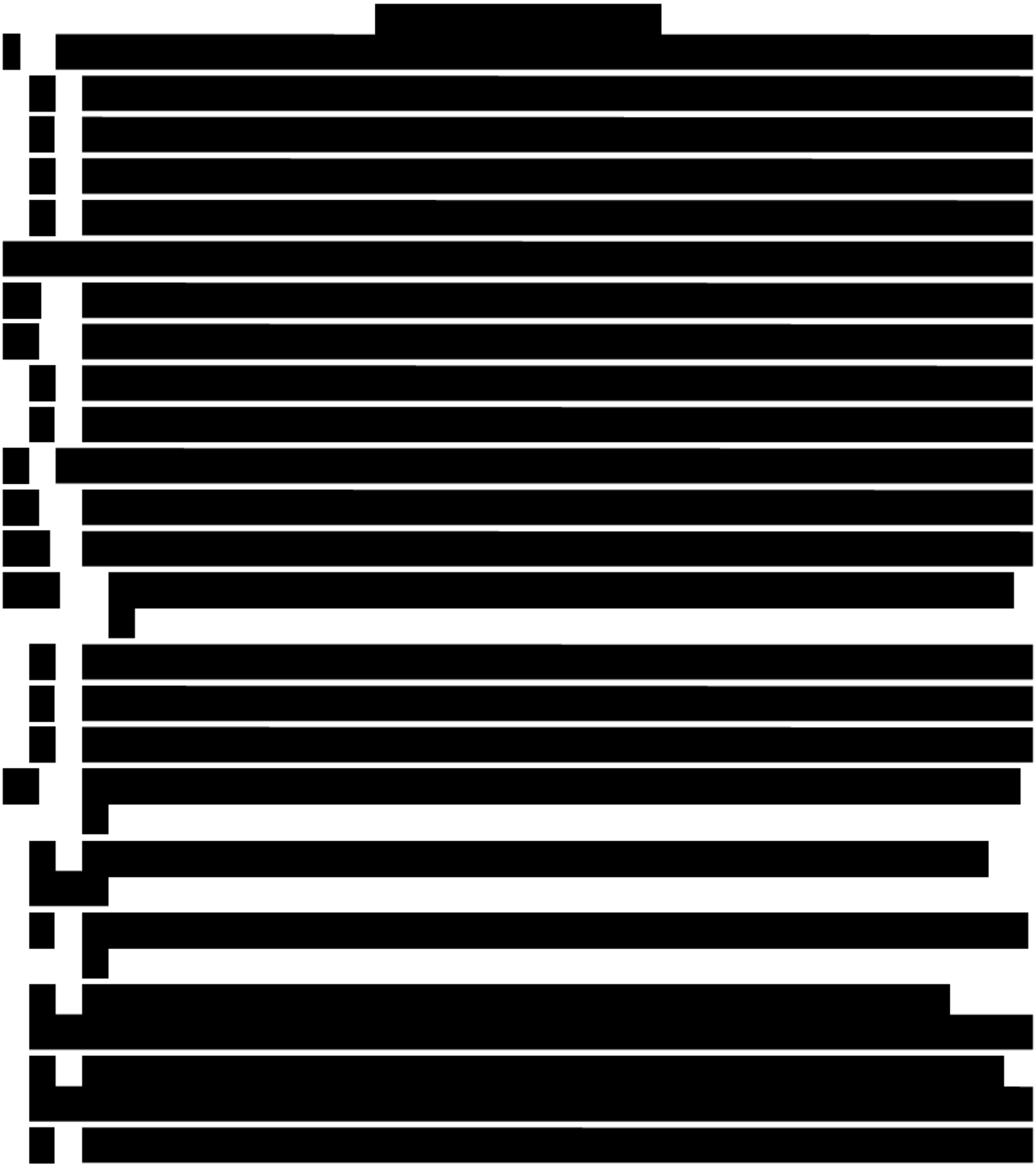
Exhibit A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH LLC, WYETH PHARMACEUTICALS LLC, PF PRISM C.V., PFIZER PHARMACEUTICALS LLC, and PFIZER PFE IRELAND PHARMACEUTICALS HOLDING 1 B.V., Plaintiffs, v. ALEMBIC PHARMACEUTICALS, LTD., ALEMBIC PHARMACEUTICALS, INC., SUN PHARMACEUTICAL INDUSTRIES LIMITED, and SUN PHARMACEUTICAL INDUSTRIES, INC., Defendants.	Redacted- Public Version C.A. No. 1:16-cv-01305-RGA CONSOLIDATED [redacted]

RESPONSIVE EXPERT REPORT OF BERNHARDT L. TROUT, PH.D.
REGARDING THE VALIDITY OF U.S. PATENT NO. 7,919,625



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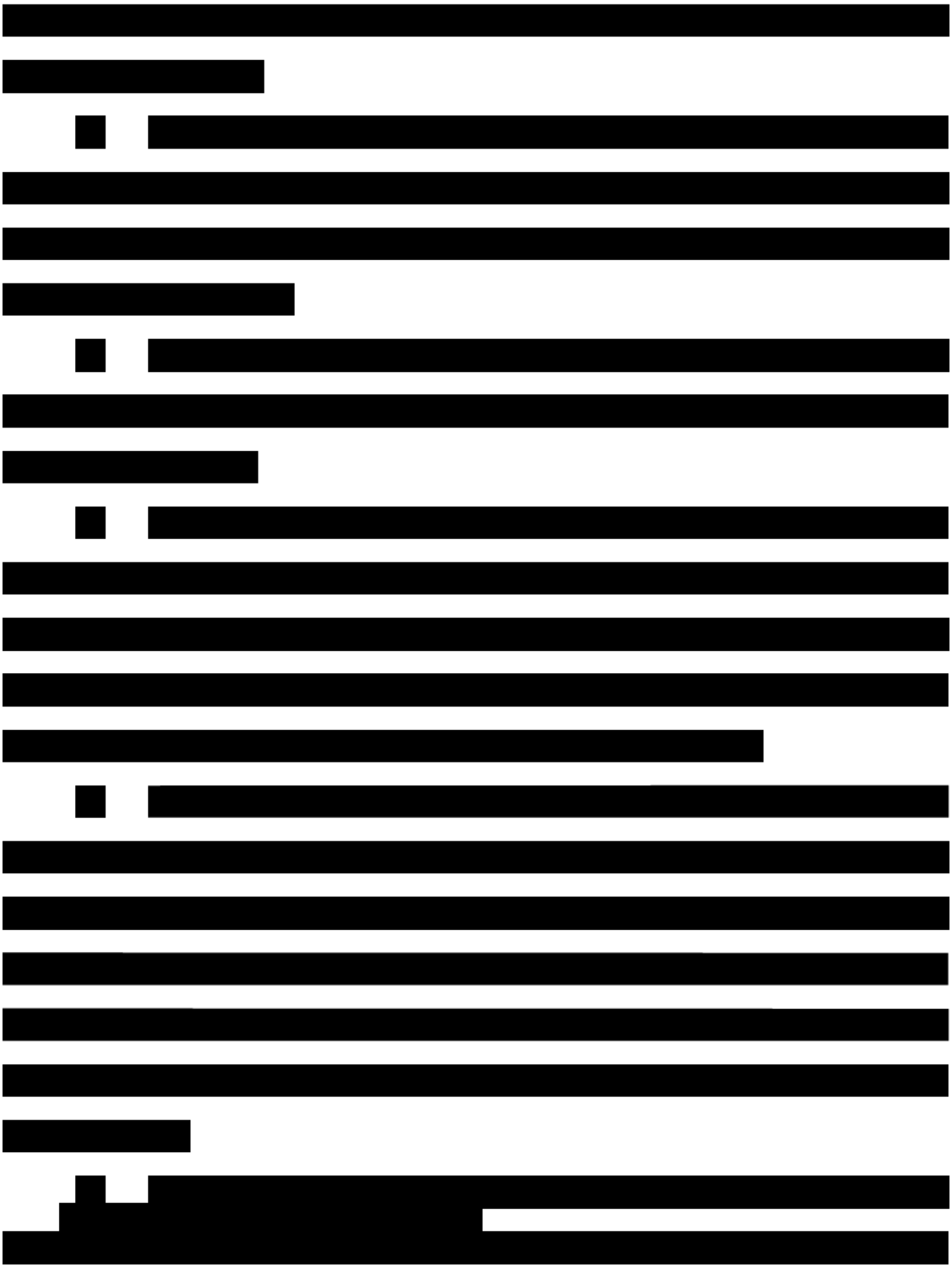
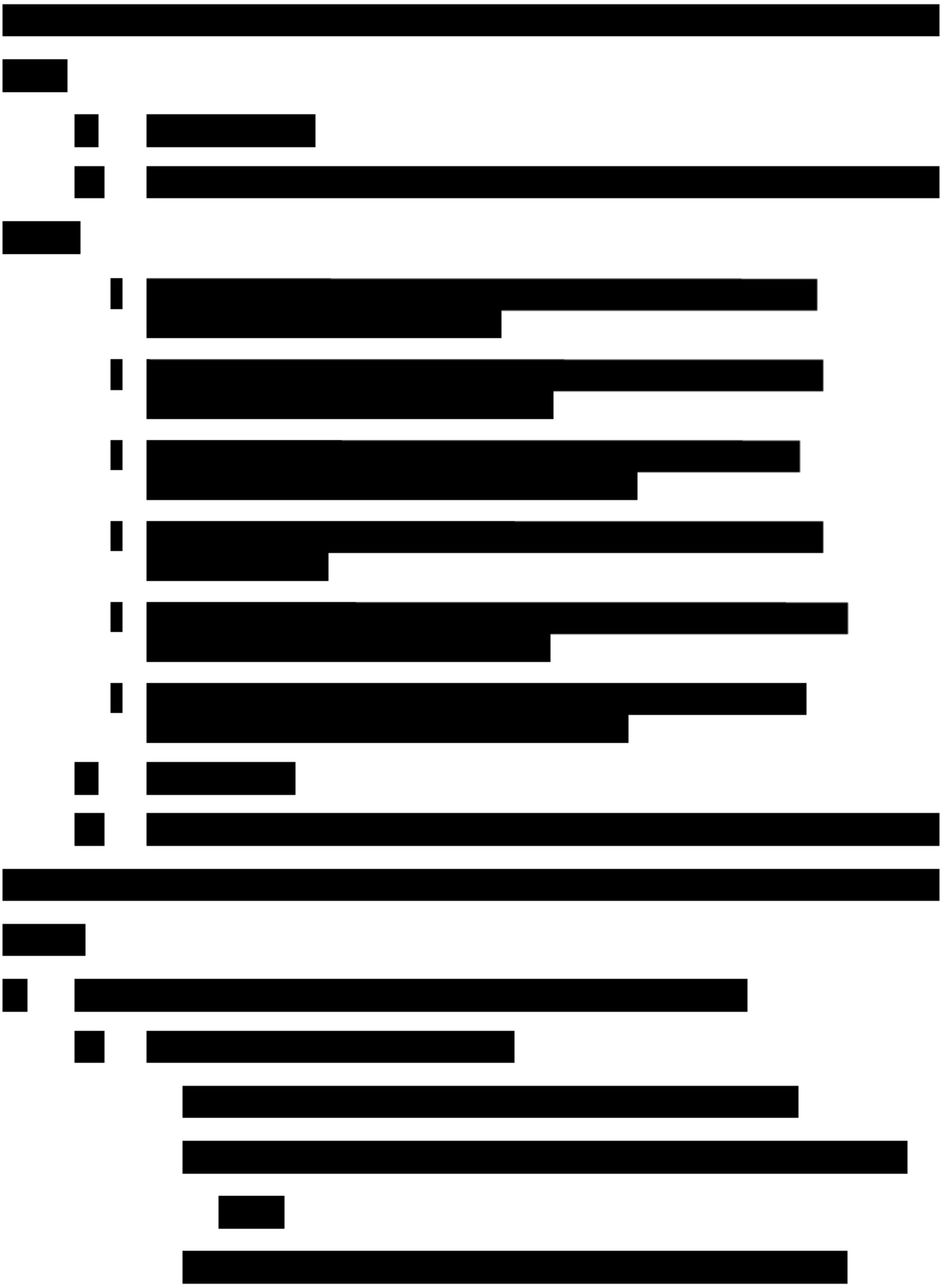




d. background on the ’625 patent; and

e. my opinion that claim 1 of the ’625 patent is not anticipated by Boschelli 2001.

III. PERSON OF ORDINARY SKILL IN THE ART

25. I understand that Pfizer has taken the position that, in the context of the ’625 patent, a POSA is:

> someone having the knowledge of (1) an M.D. with several years of experience as an oncologist treating patients with CML; (2) a Ph.D. with several years of experience conducting research on inhibition of tyrosine kinases; and (3) a person with a Ph.D. in medicinal chemistry, pharmacology, or a related field with several years of experience in drug development and formulation.

(Joint Claim Construction Br., D.I. 91, at 4 (Ex. D)).

26. I understand that Sun has further stated that in the context of the ’625 patent:

> a POSA would have a high level of skill, such as an M.D. and several years of experience as an oncologist treating patients with CML, or a Ph.D. and several years of experience conducting research on inhibition of tyrosine kinases. A POSA would have access to and could have collaborated with individuals with pertinent experience, such as a medicinal chemistry, biology, pharmacology, and/or drug metabolism and pharmacokinetics. A POSA could have a lower degree of formal education if such person had a higher degree of experience.

(Ex. D at 5).

27. It is my understanding that Pfizer and Sun do not dispute the type of experience to which a POSA would have access. In Pfizer’s proposal, a single hypothetical individual would have all of the relevant experience. In Sun’s proposal, the narrower experience of one individual would be supplemented by the knowledge of team members regarding other disciplines. My opinions are the same regardless of which definition is applied.

IV. LEGAL STANDARDS

28. I am informed that Sun has challenged the validity of the one claim set forth in the ’625 patent on several grounds including, *inter alia*, anticipation.

A. Claim Construction

29. I understand that the validity of the ’625 patent must be evaluated in light of the claim that appears in the ’625 patent as properly construed. I have read Judge Andrews’ June 27, 2018 claim construction opinion, (Markman Order, D.I. 98) (Ex. E), which construed a term in the claim of the ’625 patent as follows:

Claim Term	Court’s Construction
“pharmaceutical composition” (’625 patent claim 1)	“a pharmaceutically acceptable composition containing the specified compound and one or more excipients”

(Ex. E at 1).

30. I have applied this construction in performing the analysis in this report.

B. Anticipation

31. I have been advised by Pfizer’s lawyers that for a reference to anticipate a patent claim, it must disclose every element of that claim. The question is not whether a prior art reference suggests each element, but whether a POSA would reasonably understand or infer that every claim element is disclosed in that reference.

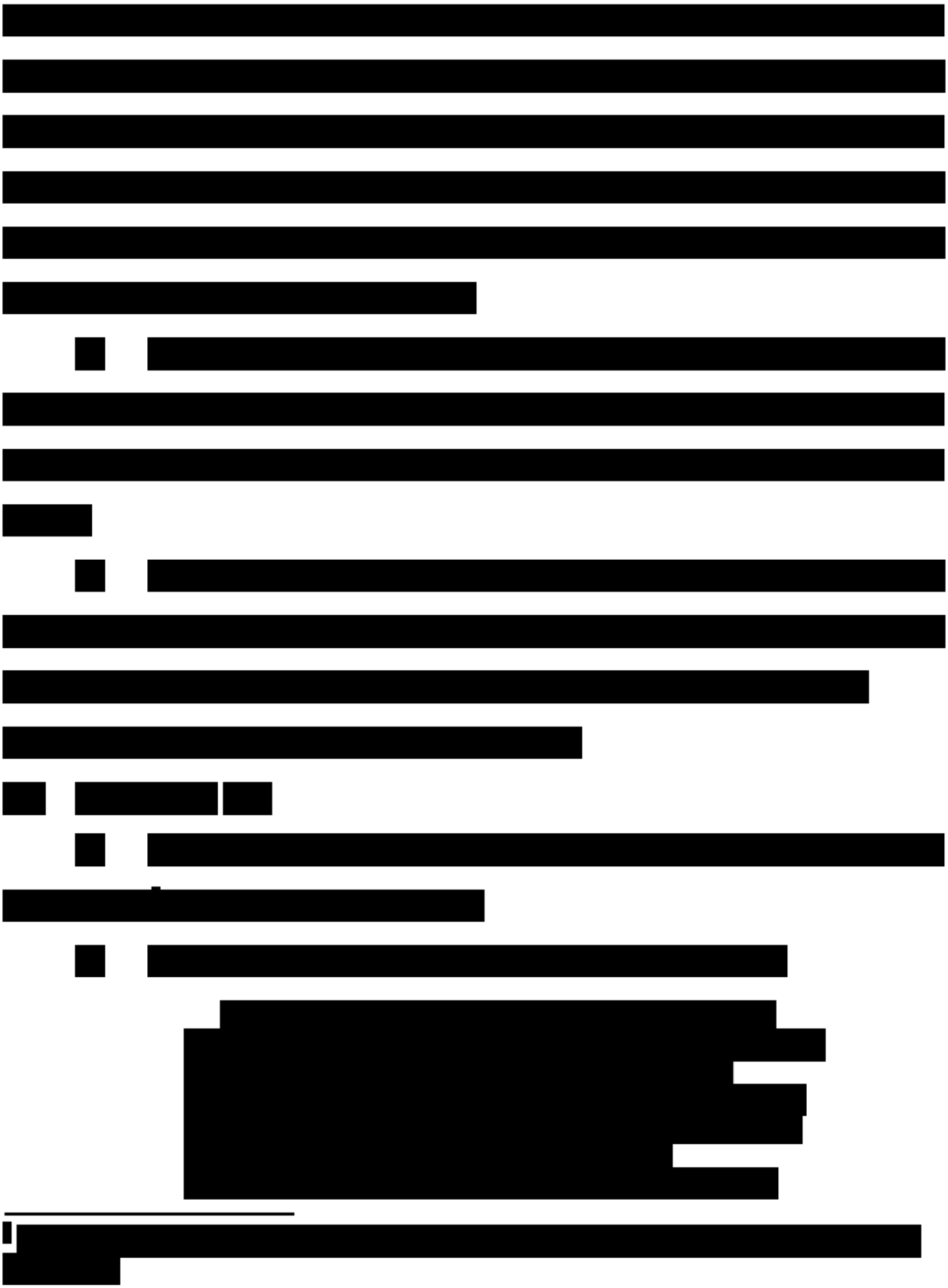
32. I further understand that, in order to anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make the invention without undue experimentation.

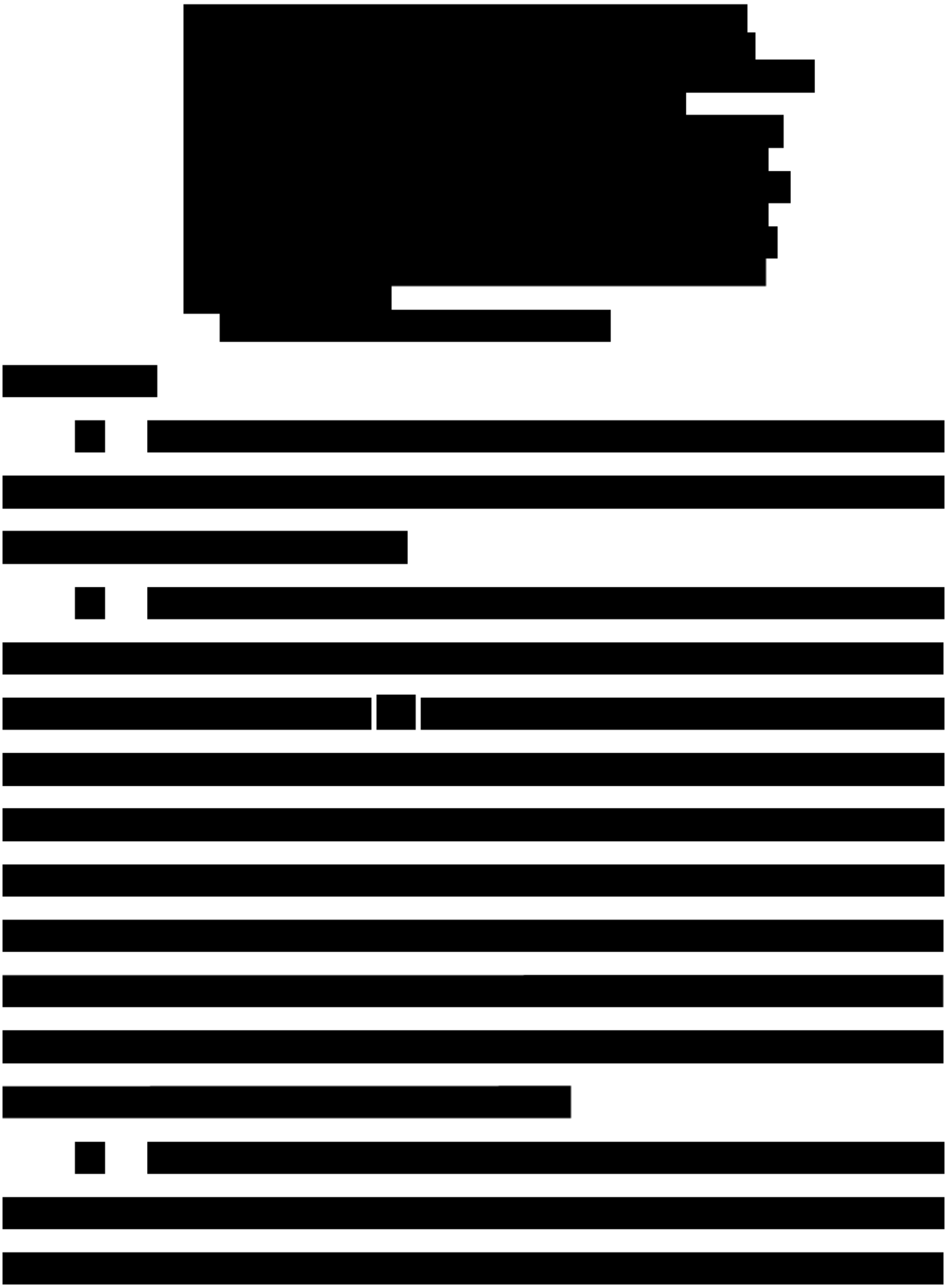
V. INFORMATION AND MATERIALS CONSIDERED

33. In preparing this report, I have reviewed and relied upon the materials listed in Exhibit F, including the materials cited and listed in this report. My opinions are based in part on my review of those documents and materials.

34. I have also relied on my education, experience, and knowledge of industry practices as well as my understanding of the applicable legal principles described above.

[redacted]





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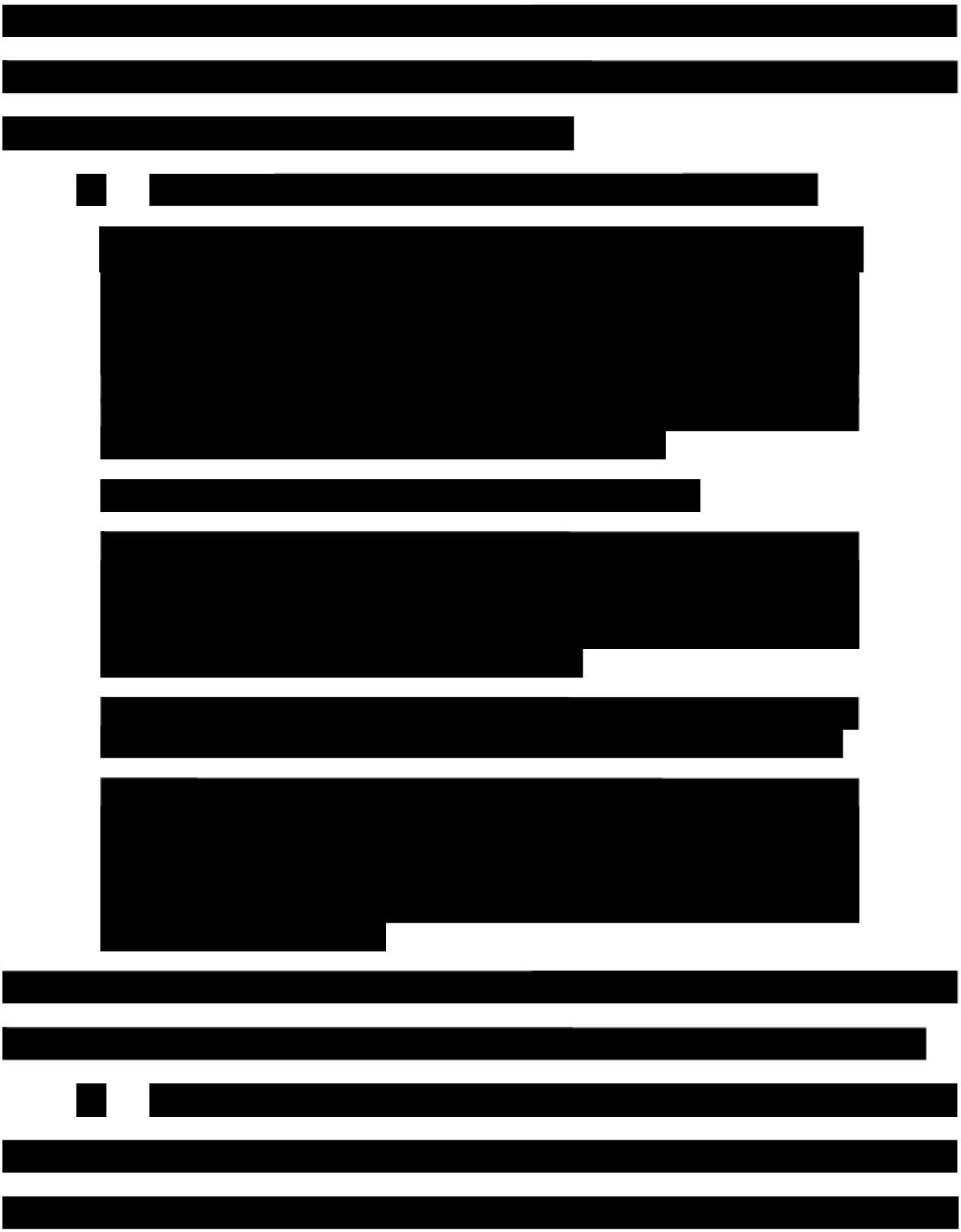

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67,377, 67,378-79 (Dec. 24, 1997) (Ex. EE). The pharmaceutical composition must also be manufactured and maintained with appropriate sterility. This is particularly important for pharmaceutical compositions that are meant to be injected. (FDA Q6A Specifications, Ex. CC § 3.3.2.3(c).; *see also Remington* ch. 41, Ex. AA at 783-84).

65. Finally, in a pharmaceutical composition the excipients used must be compatible with each other and with the API. (*Remington* ch. 38, Ex. K at 713-14). Such compatibility is essential in a pharmaceutical composition. Both dextrose and Tween-80 have incompatibilities with certain pharmaceuticals and other compounds that must be taken into account when developing pharmaceutical compositions that include those ingredients. (Arthur H. Kibbe, ed, *Dextrose, in Handbook of Pharmaceutical Excipients* 175, 176 (3rd ed. 2000) (Ex. FF); Arthur H. Kibbe, ed, *Polyoxyethylene Sorbitan Fatty Acid Esters, in Handbook of Pharmaceutical Excipients* 416, 419 (3rd ed. 2000) (Ex. GG)).

IX. CLAIM 1 OF THE ’625 PATENT IS NOT ANTICIPATED BY BOSCHELLI 2001

66. Claim 1 of the ’625 patent is not anticipated by Boschelli 2001 because Boschelli 2001 does not disclose a pharmaceutical composition comprising bosutinib.

67. As discussed above in Section VII, Boschelli 2001 discloses a newly lab-synthesized compound that is tested in animal experiments. In those animal studies reported in Boschelli 2001, human CML tumor cells were introduced into laboratory mice, and the tumors were assessed after administration of compound 31a. The mice did not have CML, and compound 31a was not being administered to provide a therapeutic benefit. The animals were to be sacrificed after testing. There is no suggestion in Boschelli 2001 that the researchers took care to develop a “pharmaceutically acceptable composition” in conducting these initial animal studies. *See Remington* ch. 10, Ex. L at 87; *Remington* ch. 39, Ex. BB at 721-22.

A. Boschelli 2001 Does Not Disclose the Synthesis of a Pharmaceutically Acceptable API

68. There is no disclosure in Boschelli 2001 that the researchers took care to synthesize compound 31a for use in the animal studies such that the active compound being evaluated would be "pharmaceutically acceptable." *See Remington* ch. 10, Ex. L at 87.

69. As explained in more detail below, the chemical synthesis disclosed in Boschelli 2001 was not designed to lead to, and likely would not have led to, a pharmaceutically acceptable API. Boschelli 2001 describes an initial laboratory procedure intended to produce a material that could be used in screening experiments. (Boschelli 2001, Ex. B at 3974). Boschelli 2001 includes no indication that there was any effort to produce compound 31a under conditions suitable for its inclusion in a pharmaceutical composition or to confirm its suitability for use in a pharmaceutical composition. *See Remington* ch. 10, Ex. L at 87.

70. A POSA reading Boschelli 2001 would conclude that compound 31a was synthesized without much attention paid to purification or to any of the specifications required for active compounds that are to be included in a pharmaceutical composition; compound 31a most likely contained impurities such that it would not have been pharmaceutically acceptable.

71. As discussed above in Section VIII.A, to be pharmaceutically acceptable, an active compound must meet specifications including a maximum of net percentage impurities and maxima of each impurity. There is no indication that the main separation step disclosed in Boschelli 2001, a basic "column chromatography," reduces impurities to pharmaceutically acceptable levels. (Boschelli 2001, Ex. B at 3974). Indeed, this separation method is not used for creating pharmaceutically acceptable actives, but rather is used only for a crude separation. When creating a pharmaceutically acceptable active, appropriate particle size and type, pressure, column length, and flow rate must all be taken into account during the separation step. Crude

column chromatography of the kind used in Boschelli 2001 does not take these factors into account. *See* A.M. Katti & P. Jagland, *Development and Optimization of Industrial Scale Chromatography for Use in Manufacturing*, 26 Analusis Mag. 38, 45-46 (1998) (Ex. HH) (discussing the conditions which must be optimized for using the chromatography process past the discovery stage). Additionally, the large range of the melting point of compound 31a reflects a large fraction of impurities in the compound. *See* Steven A. Hardinger, *A Simple Demonstration of the Effect of Impurities on Melting Point*, 72 J. Chemical Educ. 250, 250 (1995) (Ex. II).

72. Further, Boschelli 2001 does not reflect any measurement or characterization of the impurities in compound 31a or otherwise suggest that the specifications required for a pharmaceutical composition were met. *See* FDA Q6A Specifications, Ex. CC at §§ 3.2–3.3; *see also Remington* ch. 36, Ex. M at 669; Leonard C. Baily, *Ch. 33: Chromatography, in Remington: The Science and Practice of Pharmacy* 587, 587 (Alfonso R. Gennaro et al. eds., 20th ed. 2000) (Ex. JJ). The only characterization done of compound 31a, other than of its melting range, was aimed at confirming that compound 31a was in fact the compound the researchers had intended to synthesize. (Boschelli 2001, Ex. B at 3974).

73. Boschelli 2001's lack of attention to the impurity levels in compound 31a is also apparent in the filtration step of the synthesis. Boschelli 2001 describes the use of the solvents methanol and dichloromethane, also known as methylene chloride, in synthesizing compound 31a. (Boschelli 2001, Ex. B at 3974). The FDA categorizes both methanol and dichloromethane as Class 2 solvents and requires strict concentration limits of these solvents in pharmaceutical compositions. *See* FDA Q3C Impurities, Ex. EE at 67,381, Table 2. There is no indication in Boschelli 2001 that the methanol and dichloromethane left in the compound as residual solvents

were removed during the filtration step through drying. Boschelli 2001 also fails to mention any testing done to determine whether the residual solvent levels in compound 31a fell below acceptable limits.

B. Boschelli 2001 Does Not Disclose the Use of Pharmaceutically Acceptable Excipients

74. In addition to failing to disclose the creation of a pharmaceutically acceptable active compound, Boschelli 2001 does not disclose that the researchers took care to procure and use pharmaceutical grade excipients when preparing the composition administered in the reported animal studies. Specifically, nothing in Boschelli 2001 suggests that the inactive components of Tween-80, dextrose, and water included with compound 31a in the formulation administered to the laboratory mice were pharmaceutical grade or would have been pharmaceutically acceptable as used. *See Remington* ch. 10, Ex. L at 87; *Remington* ch. 39, Ex. BB at 721-22. As discussed above in Section VIII.B, paragraph 62, the rigorous USP-NF standards required for components of pharmaceutical compositions need not apply to the use of compounds for tests involving laboratory animals. (Wolff 2003, Ex. T at 34). Compositions used for tests involving laboratory rodents may be made with laboratory grade materials.

C. Boschelli 2001 Does Not Disclose the Use of Procedures Required for Making Pharmaceutically Acceptable Compositions

75. There is no indication in Boschelli 2001 that the researchers that conducted the animal testing followed production procedures that would have produced an aqueous-based pharmaceutically acceptable composition. *See Remington* ch. 41, Ex. AA at 781.

76. As discussed above in Section VIII.B, paragraph 60, the water used in pharmaceutical compositions, particularly those formulated for injection, must meet rigorous standards to the ensure sterility of the composition. *See* USP25-NF20 Water, Ex. Z at 1809-10;

[redacted]

[redacted]

Exhibit B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
Civil Action No. 16-1305-RGA

----------X

WYETH LLC, WYETH PHARMACEUTICALS INC.
et al.,

Plaintiffs,

-against-

ALEMBIC PHARMACEUTICALS, LTD., et al.,

Defendants.

----------X

** CONFIDENTIAL **

VIDEOTAPED DEPOSITION OF BERNHARDT TROUT, Ph.D.

New York, New York
Wednesday, August 7, 2019

Reported by:
JEFFREY BENZ, CRR, RMR
JOB NO. 165308

August 7, 2019
9:04 a m.

Videotaped Deposition of BERNHARDT TROUT, Ph.D., held at the offices of Freeborn & Peters LLP, 230 Park Avenue, New York, New York, before Jeffrey Benz, a Certified Realtime Reporter, Registered Merit Reporter and Notary Public of the State of New York.

APPEARANCES:

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KIMBERLY BEIS, ESQ.

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Attorneys for Defendant Alembic Pharmaceuticals, Ltd., et al.
2099 Pennsylvania Avenue, NW
Washington, D.C. 20006
BY: APRIL WEISBRUCH, ESQ.

ALSO PRESENT:
PHIL RIZZUTI, Videographer

THE VIDEOGRAPHER: This is the start of Media labeled Number 1 of the video-recorded deposition of Bernhardt Trout in the matter of Wyeth LLC, Wyeth Pharmaceuticals Inc., et al., versus Alembic Pharmaceuticals Ltd., et al., in the United States District Court for the District of Delaware, Case Number 16-1305-RGA. This deposition is being held at 230 Park Avenue, New York, New York, on August 7, 2019, at approximately 9:04 a.m.

My name is Phil Rizzuti. I am the legal video specialist from TSG Reporting Inc. The court reporter is Jeff Benz, in association with TSG Reporting.

Counsel, please introduce yourselves.

MR. BENSON: Stephen Benson, from the firm of Freeborn & Peters, on behalf of the Sun defendants.

MS. BEIS: Kimberly Beis, also from Freeborn & Peters, on behalf of the Sun defendants.

MS. WEISBRUCH: April Weisbruch, from Sheppard, Mullin, Richter & Hampton, here

on behalf today of Alembic.

MS. PIPER: Stephanie Piper, from Arnold & Porter, here on behalf of the plaintiffs.

THE VIDEOGRAPHER: Will the court reporter please swear in the witness.

BERNHARDT TROUT, Ph.D.,
called as a witness, having been first duly sworn by Jeffrey Benz, a Notary Public within and for the State of New York, was examined and testified as follows:

EXAMINATION BY MR. BENSON:

Q. Good morning, Dr. Trout.

A. Good morning.

Q. As you heard during the introductions, my name is Stephen Benson, and I represent the Sun defendants.

And I understand from looking at your CV that this is not your first time being deposed, correct?

A. Correct.

Q. Okay. So I'm not going to go into details about the structure of a deposition,

with the understanding that you're familiar with that. However, I will just remind you that giving deposition testimony is equivalent to giving testimony in a court of law, the same requirements for truthfulness and the same requirement that you answer completely, to the extent that you're able, any question that is asked. Do you understand those rules?

A. Yes.

Q. Okay. And if you don't understand a question, please feel free to let me know. If you want me to rephrase the question, we can do that as well. Okay?

A. Okay.

Q. And lastly, if you need to take a break, just let me know. I'm happy to accommodate that. Okay?

A. Thank you.

Q. Great.

Now, you -- at some time in your engagement in this matter you received an expert report by a Dr. Craig Lindsley; is that correct?

A. Yes, I -- I think I received two reports --

Q. Okay.

A. -- from Dr. Lindsley.

Q. Okay. And an opening report that related to the invalidity of the -- let's see, U.S. Patent Number -- let me get the full number on the record.

7,919,625, correct?

A. Yes. I think his report discussed a number of patents but that was the focus of my analysis.

Q. Okay. And for the purposes of this deposition, I'll refer to that particular patent as "the '625 patent." Okay?

A. Okay.

Q. Now, did you read the entirety of that opening report of Dr. Lindsley?

A. Yes.

Q. Okay. And my understanding, based on looking at your own report, is that your opinions are specifically focused on one opinion provided by Dr. Lindsley relating to the anticipation of the '625 patent; is that correct?

A. Broadly, I'm not sure if that's one

opinion or if it's multiple opinions. But, yes, the focus was the anticipation of the '625.

Q. All right. Now -- were you asked to opine on any of the other bases of invalidity presented by Dr. Lindsley in his opening report?

A. No.

Q. Okay. Do you have any understanding as to why you were asked specifically to address just the anticipation argument as it relates to the '625 patent?

A. No broader understanding. I just know about the '625 and the opinions in my report.

Q. Okay. Having read Dr. Lindsley's opening report, do you feel you were qualified to address any of the other opinions Dr. Lindsley presented as it relates to invalidity of the '625 patent?

MS. PIPER: Objection. Outside the scope of Dr. Trout's report and opinion.

A. My focus and my task, as I outlined in my expert report itself, was on the '625, so I didn't really look into the details of the others.

Q. Okay. I think my question was just a

little bit simpler. It wasn't asking you to give an opinion. It's as to whether or not you were able to determine, based on your review, whether you were qualified to opine on the issues presented in the remaining portions of Dr. Lindsley's opening report?

MS. PIPER: Objection. Outside the scope of what Dr. Trout was asked to consider.

A. I didn't look at it to the extent that I could analyze whether I was qualified or not. I -- I think that I'm qualified to give the opinions that I gave in my report.

MR. BENSON: Okay. All right. And in -- why don't we go ahead and -- we have previously marked a binder here as the -- Trout Exhibit Number 1, and I will have the court reporter hand that to you.

(Dr. Trout's expert report, including exhibits, was marked Trout Exhibit 1 for identification, as of this date.)

THE WITNESS: Thank you.

Q. And I will represent to you that this is a copy of your expert report that you've

provided in this case, along with the exhibits cited therein. But to -- to convince yourself that I am correct, why don't you go ahead and look at the report here, and let me know if you agree that that appears to be the report you provided in this case.

A. So I flipped through the report in Tab 1, and it looks like -- I mean, just on a high level it looks like my report.

Q. Okay. Now, you -- after providing your expert report, you are aware that Dr. Lindsley prepared a reply report in response to that, correct?

A. Yes.

Q. And did you have an opportunity to read that report?

A. Yes.

Q. Okay. And after reading that report, have any of the opinions expressed in your opening report or your response report changed?

A. No.

Q. Okay. Did you formulate any additional opinions based on your reading of Dr. Lindsley's reply report?

A. No, not based on what was in my report. I mean, those are the opinions in my report, and so I stick to those opinions that I gave.

Q. Okay. Is there anything at all you would want to supplement today with respect to your own opinions that you've not shared with defendants?

A. Not at this point in time.

Q. Okay. Fair enough. All right.

So if I could direct you to your -- your expert report, paragraph 25, please. And this is the definition of a person of ordinary skill in the art.

Now, based on your report, you have an understanding, your own definition of a person of ordinary skill in the art is a little different from that presented by Dr. Lindsley, correct?

A. Yes, there's a little bit of a difference, and I discuss that in paragraph 27.

Q. Right. But basically -- my understanding from your report is, your opinions wouldn't change were you to adopt Dr. Lindsley's

definition of a person of ordinary skill in the art, correct?

A. Yes.

Q. And now, with respect to your own opinion about a person of ordinary skill in the art, first you believe that such a person would have knowledge that would be possessed of an MD with several years of experience as an oncologist treating patients with CML, correct?

A. That's part of the -- the knowledge of that P-O-S-A.

Q. And for clarity, CML is an abbreviation for chronic myelogenous leukemia; is that correct?

A. That's my understanding.

Q. Okay. And for the court reporter, myelogenous is spelled M-Y-E-L-O-G-E-N-O-U-S. And I make no representations as to whether or not I'm pronouncing that correctly.

Do you have any experience with the treatment for CML?

A. No, not outside of just reading the documents in this case.

Q. Okay. So what was your understanding

of CML prior to your engagement in this case?

A. I didn't have a -- a specific or detailed understanding. I knew broadly about Gleevec is one of the pharmaceuticals, but I didn't know much about CML per se.

Q. Okay. And what, if anything, did you know about Gleevec? Was it just generally that it was a medicine for treating CML?

A. Yes, that it's an important medicine for treating, you know, leukemia or cancer diseases.

Q. Now, did you review that portion of Dr. Lindsley's opening report wherein he talked about CML?

MS. PIPER: Objection. Outside the scope of what Dr. Trout was asked to opine on.

A. Yes, I reviewed his entire report.

Q. And I think the question was simply, you did review that portion. Is there anything about that, in reading about Dr. Lindsley's description of CML, that you disagreed with?

MS. PIPER: Objection. Outside the scope of what Dr. Trout was opine -- was

said to opine on.

A. I don't have any opinions about that part of the report.

Q. Okay. Okay. How did -- in this case, how did you gain your understanding of CML?

A. I gained my understanding from the '625 patent, I mean, to the extent that I have an understanding, and from just the background that I read in Dr. Lindsley's report and maybe in some of the other documents as exhibits. But I think that the main focus was the '625, a few of the papers, a few of -- in the exhibit -- my exhibits, and then Dr. Lindsley's report -- reports.

Q. With respect to Dr. Lindsley's reply report, did you focus on any section other than that portion of his report that was replying to your own opinions?

MS. PIPER: Objection. Outside the scope of what Dr. Trout was asked to opine on.

A. I read the whole report, but, no, my -- I think your question was about focus. My focus was on the paragraphs and other parts

related to my opinions.

Q. Okay. Okay. Returning very briefly to your definition of a person of ordinary skill in the art, it also includes the opinion that a person of skill in the art would have the knowledge of a person having a Ph.D. with several years of experience conducting research on inhibition of tyrosine kinases, correct?

A. Yes, that's one of the parts to the -- to the definition, yes.

Q. Okay. What, if any, experience do you have conducting research on inhibition of tyrosine kinases?

A. None, except -- not doing research, I mean, just broad background reading from my general knowledge, but not specific experience doing research.

Q. Can you kind of describe to me what your background knowledge is of just, you know, inhibition of tyrosine kinases?

A. Yes. Well, I studied biochemistry as an undergraduate. I continued learning about cellular biology and protein biochemistry post-undergraduate, certainly as an independent

researcher when I joined MIT on the faculty in 1998, so I continued to gain knowledge in that area. And I understand and continue to learn about drug development and inhibition broadly so I have this kind of general understanding.

Q. So is it fair to say your understanding of the inhibition of tyrosine kinases is not specifically as it relates to the treatment of CML?

A. Yes, that's correct.

Q. What, if any, understanding do you have about the role of the inhibition of tyrosine kinases in the treatment for CML?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. I just have broad understanding based on the background that I just described and the documents that I reviewed.

Q. So prior to your engagement in this case, did you have any understanding of how tyrosine kinases and/or their inhibition were implicated in CML therapy?

A. Again, just very broadly. Nothing specific about that, no.

Q. All right. And lastly, your opinion regarding the knowledge of a person having ordinary skill in the art includes a person with a Ph.D. in medicinal chemistry, pharmacology, or a related field with several years of experience in drug development and formulation, correct?

A. Yes. Correct.

Q. Okay. Now, what, if any, experience do you have -- can you -- well, strike that.

Can you describe for me your experience in drug development and formulation generally?

A. Yes. As an undergraduate at MIT in the '80s, I worked on research related to processing of pharmaceuticals and also enzymatic catalysis. I went on to do a Ph.D. in chemical reactivity. And then when I joined the MIT faculty in 1998, I began an independent research program focusing on formulation -- well, say, drug development and formulation broadly. And so I have continued that research up till today. I can go into all levels of detail as you like.

Q. Your researches into drug development and formulation, are they aimed at specific

chemical compounds? For example, you know, active pharmaceutical ingredients, for example?

A. Yes. To qualify that, the broad focus of my research is to develop new technologies related to drug development, formulation, and manufacturing. In doing that we work on specific pharmaceuticals, a range of pharmaceuticals.

Q. Just for clarity, how do you define the term "pharmaceutical"?

A. And you're talking about general, not in the specific context, like --

Q. Just generally --

A. -- talking about the patent but just generally?

Q. Yes. I think you said, you know, you do work on specific pharmaceuticals, a range of pharmaceuticals. So, you know, when you're using it just generally in that sense, what is your understanding of -- what is your definition of a "pharmaceutical" as you use it there?

A. In that particular sense I was addressing your question which I interpreted as a -- a specific API, or active pharmaceutical

ingredient, so the active ingredient I guess in a formulation or outside of a formulation.

Q. So a medicinal drug, for example?

MS. PIPER: Objection to form.

A. I guess I would stick with the terminology that I used.

Q. Okay. Now, you'll agree with me a person of ordinary skill in the art, as you've defined it, would understand a pharmaceutical composition to include an API, or active pharmaceutical ingredient, right?

A. Yes.

Q. And a person of ordinary skill in the art would also understand a pharmaceutical composition could include one or more excipients as well, correct?

A. Yes. And, again, I want to qualify, I know that's a term that has specific implications in this case. And I understand we're just speaking broadly. So outside of the context of, let's say, a specific term in a claim, yes.

Q. Okay. So generally speaking, just to rehash, and, again, just speaking generally, a

person of ordinary skill in the art, in your opinion, hearing the term "pharmaceutical composition" would think of an API and one or more excipients, right?

A. Yes, broadly speaking. Again, I -- that seems to be a term that's a little bit more used in a legal context than, let's say, a technical context. But if I put it into a technical context, then, yes.

Q. So is it -- I'm -- just so I understand, is it -- are you saying that that term like a "pharmaceutical composition" isn't typically used in the art, like, the pharmaceutical arts or the drug development field? Or you're just saying that it's used both in a legal context here but also in a -- I'm just trying to understand.

MS. PIPER: Objection to form.

A. So it can be used in both contexts.

Q. Okay.

A. In sort of my daily -- daily basis we -- or daily work we typically would talk about a drug product or a drug formulation. Composition or pharmaceutical composition can

also be used. Just I know it tends to be used more in the legal context, and certainly in this case, so I wanted to make that clear.

Q. Okay. I appreciate that. Thank you. And I think I'm clear on that now.

Okay. So do you consider yourself to be a person having ordinary skill in the art based on your own definition?

A. And just to clarify, you're asking about the entire definition?

Q. Correct.

A. No. I think my skill is really focused on the third part of that definition.

Q. Okay. Let me direct you to paragraph 42 of your report, please. Now, you've reproduced here the single claim of the '625 patent, correct?

A. Yes.

Q. And that's as it appears in the patent itself, right?

A. Unless I've made any typos, yes.

Q. And so we agree that the compound that is referenced here in Claim -- Claim 1 of the '625 patent is bosutinib, correct?

MS. PIPER: Objection to form.
A. Yes, that's my understanding.
Q. Okay. And you don't disagree with Dr. Lindsley in that regard, right?
MS. PIPER: Objection to form.
A. No. As far as I understand it, that's correct.
Q. Okay. Now, I see here that -- well, so the claim is, you know, giving -- you know, replacing the actual chemical name with bosutinib, the claim states, "A pharmaceutical composition comprising a CML inhibiting amount of the compound bosutinib."
Correct?
A. Yes.
Q. Okay. Now, looking at Footnote 1, which is on the bottom of page 9, you observe here, in your opinion, that the '625 patent uses treating and inhibiting CML interchangeably. You see that?
A. Yes.
Q. Okay. And in formulating your opinions, did you also view treating CML and inhibiting CML as interchangeable terms?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
A. That's what I included here in the background as I understand it. Yes.
Q. Well, the question here is, did you use that -- those terms interchangeably, or are you simply observing that you believe that the '625 patent does so?
A. I'm observing that I think the '625 patent does so.
Q. Okay. So what is your understanding of what a CML inhibiting amount of bosutinib would mean?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
A. I don't have an opinion on that.
Q. Okay. So for clarity, you don't have an opinion as to -- well, let me ask you a different question.
In formulating your opinions, what was your understanding of what a CML inhibiting amount of bosutinib meant?
MS. PIPER: Objection. Outside the scope of what Dr. Trout was asked to opine

on.
A. I didn't formulate opinions specifically on that.
Q. Okay. Okay. Now, you understand that the term "pharmaceutical composition" in -- as it appears in Claim 1 has been construed by the Court, correct?
A. Yes.
Q. And you provided that construction in your opinion at paragraph 29, correct?
A. Yes.
Q. Okay. And it is your understanding the Court's construction of "pharmaceutical composition" is, "A pharmaceutically acceptable composition containing the specified compound and one or more excipients."
Correct?
A. Yes.
Q. Okay. And in this construction, your understanding of a -- "the specified compound" is bosutinib, correct?
A. Yes.
Q. Okay. And --
A. Meaning -- sorry, just to qualify.

That's the other part of the -- that's another element of the claim, right --
Q. That's correct.
A. -- yes.
Q. And so your understanding is when -- when the Court is -- in the Court's construction when it says, "A pharmaceutically acceptable composition containing the specified compound," it's your understanding based on the claim that that specified compound in this context is bosutinib, correct?
A. Yes, in the context of Claim 1 of the '625, correct.
Q. And one or more excipients, right? Is the last portion of this construction.
So what is your understanding of what an excipient would be in the context of this construction?
A. So I talk about that, for example, on page 15 of my report, paragraph 53. I say, "There are ingredients other than the active ingredient," and then there's some, you know, more qualification of that in the subsequent paragraphs in terms of specific types of

specifications that they must meet.

Q. Now, you don't disagree generally that TWEEN 80 is -- can be an excipient in a pharmaceutical composition as -- as you've defined excipients here, right?

MS. PIPER: Objection to form.

A. It can be an excipient. It has to meet the kind of specifications that I discuss here, a particular version of TWEEN 80, but it can be.

Q. Okay. And, in fact, it's described in the '625 patent as a possible excipient for bosutinib compositions, correct?

A. And just to be clear, could you point me to where you're referring?

Q. Yes, I can. Let me direct you to Exhibit A.

Sorry, my computer is asking me if I'm enjoying the iAnnotate app that I'm using right now, so I had to take care of that and let it know I was indeed enjoying it, so. It wouldn't leave me alone about it.

So, I'm sorry, we were going to Exhibit A, which -- in responding to their

inquiry.

Closed it for me.

Okay. So this is the '625 patent. Do you recognize that?

A. I mean, looking at the first page it looks like the '625 patent that I'm familiar with, yes.

Q. Okay. So let's go to Column 4, beginning at line 5, and let me know when you're there.

A. I'm there.

Q. Okay. Now, this begins with, "The compounds of the invention may be formulated with conventional excipients such as a filler, a disintegrating agent, a binder, a lubricant, a flavoring agent, color additive, or a carrier."

Right?

A. Yes.

Q. And then here in this section various types of excipients are described. Would you agree with me on that?

A. Yes, in the subsequent part of that paragraph.

Q. And if we go to that paragraph that

begins around line 27 in Column 4, do you see that?

A. Yes.

Q. And here within this -- in this it states that, "Detergents such as TWEEN 20 and TWEEN 80 can be used in certain formulations of the invention."

Correct?

A. Yes. I think you're referring to lines 34 to 35 in that Column 4.

Q. Yes. Correct. Okay. So you will agree with me that the patent itself identifies TWEEN 80 as a pharmaceutical excipient that could be used in bosutinib compositions, correct?

A. Yes. And I emphasize that this is within the context of the '625 patent --

Q. Okay.

A. -- which we're talking about pharmaceutical compositions.

Q. Okay. Perfect.

Now, some other -- some other excipients that are mentioned here generally, so -- for example, if we go back up a little bit

further to line 17, wherein it states, "When provided orally or topically."

Do you see that paragraph?

A. Yes. Yes.

Q. Okay. You know, it says: When provided orally or topically some -- such compounds would be provided to a subject by deliver -- by delivery in different carriers. And then it says, "Typically such carriers contain excipients such as starch, milk, sugar," and then it goes on and identifies some others, correct?

A. Yes.

Q. And you'll agree with me that dextrose is a sugar, correct?

A. Yes.

Q. And dextrose is a well-known excipient for use in pharmaceutical compositions, wouldn't you agree?

MS. PIPER: Objection to form.

A. Well, I would say that dextrose is in, for example, the Handbook of Pharmaceutical Excipients. So I assume you're talking about the timeframe of the '625 patent.

Q. Correct.
A. So it was known as an excipient, for example, in the Handbook of Pharmaceutical Excipients in that timeframe.
Q. Okay. And you reference the Handbook of Pharmaceutical Excipients, correct?
A. Yes.
Q. Okay. And the Handbook of Pharmaceutical Excipients is -- you'll agree with me is a handbook that identifies various pharmaceutical excipients that can be used in pharmaceutical compositions, correct?
A. Well, I would say it's a handbook, so it has entries on a set of pharmaceutical excipients, including selective but important properties that the formulation scientist or someone interested would need to know for its use as an excipient, including reference to various specifications beyond what's in that handbook.
Q. Okay. Do you have any understanding as to whether or not excipients are identified in the Handbook of Pharmaceutical Excipients that have never been used in pharmaceutical

compositions approved by FDA?
A. I haven't checked all the excipients.
Q. Okay.
A. I presume they have been used, but I haven't checked them one by one.
Q. And do you have any understanding as to whether or not dextrose itself has been used in formulations of drugs that have been approved by FDA?
A. By the date of the '625 patent I presume you're talking about.
Q. Yes.
A. I can't think of an example sitting here. I have no reason to think that it wasn't used in other formulations, but I can't think of an example.
Q. Are you aware of a database that FDA maintains that identifies excipients that have been used and approved in drug products previously?
MS. PIPER: Objection to form.
A. Yes, I know there's a list.
Q. And do you know what the name of that list is?

A. Yes. It's called the GRAS list, I think is what you're talking about. At least that's what I'm thinking of.
Q. GRAS list?
A. Yes. It's a -- abbreviation for Generally Recognized As Safe.
Q. Do you have any understanding as to whether or not dextrose is identified as a -- an excipient in the GRAS list?
A. I didn't specifically look it up in the GRAS list.
Q. Would you expect it would be identified there, based on your experience and knowledge?
A. I would think it would be identified there, but one would have to check to confirm.
Q. Okay. How about TWEEN 80? Would you expect TWEEN 80 would be identified in the GRAS list as well, based on your experience and knowledge?
A. Yes, again, I would expect it. I didn't specifically check it as of this date, as of the date of the '625 patent.
Q. And I appreciate your clarifications

but I will confirm for you, just to simplify things, that if I'm asking you a question about this -- something in -- being known in the art, I am referring to known as of the priority date of the invention. Okay?
A. Okay.
Q. So if I'm going to deviate from that, I'll let you know. Okay.
A. Okay.
Q. But, again, I do appreciate your -- your being clear about that when I ask a question. It's helpful.
Now, other carriers that are identified in Column 4 of the '625 patent, for example, at line 14 are carriers such as water, correct?
A. Yes, water is identified there.
Q. Okay. And there's really no dispute that water is a common carrier for pharmaceutical compositions, right?
MS. PIPER: Objection to form.
A. Yes. I mean, certain water that has to meet specifications for it to be used in a pharmaceutical composition. But it's possible,

yes.

Q. All right. Let's talk a little bit about various modes of administration the '625 patent identifies for the pharmaceutical compositions of the invention. And I will direct you now, again staying in Exhibit A, Column 3 and line 52.

Now, do you see here where it states that the compounds may be provided orally, by intralesional, intraperitoneal, and there are various modes of administration identified, correct?

A. Yes.

Q. Okay. And, again, one of those identified here at -- looks like line 53 is intraperitoneal, right?

A. Yes.

Q. And what is intraperitoneal?

A. It means delivery into the body cavity, so not into the blood system, circulatory system directly, for example.

Q. Okay. Is that often abbreviated as ip, little i, little p?

A. I've seen it abbreviated as such.

Q. Okay. Now, what is your understanding, if you have any, of what form of compositions are typically administered ip, or intraperitoneal?

A. What do you mean by "form"?

Q. Sure. So, for example, powders, tablets, solutions, suspensions, you know, what form of composition are typically administered intraperitoneal?

A. And speaking just generally, I would think typically it would be injected, and so it would have to be some kind of liquid or suspension.

Q. Okay. You said "liquid" or "suspension." Are those, in your mind, different things?

A. Yes. A liquid in that context, it is more broad. Suspension is specifically a liquid with solid material in it.

Q. Okay. So is it fair to say then, based on that testimony, that liquid, in your mind, is more something that -- where all of the various excipients are in solution versus a suspension where some of those excipients are

suspended in the liquid matrix?

A. Yes, that's what I was thinking of in general context. It might differ depending on the specific context in which it's used.

Q. Are there any other forms of compositions or -- or that you're aware of that are delivered intraperitoneal?

A. There's none that I'm aware of. Those are the broad categories. This is a big field. Lots of people do research. Someone may have -- pretty confident that people -- someone must have tried other different types of forms, but the ones I gave you I think would be generally the ones used.

Q. Okay. Great.

Now, in your own research, do -- do you have an opportunity to use laboratory animals in your research?

A. I do not use laboratory animals in my laboratory. I certainly work with other people who use them and review literature and the results of those as I need them, but I do not in my lab do animal research.

Q. Have you ever in your career or

education had an opportunity to work with laboratory animals?

A. So personally I have not done experiments on laboratory animals. I have helped to design studies that were done on laboratory animals and interpret the results. But that was -- since '98 when I started my independent career, so I generally have students and technicians and other people do that kind of research.

Q. Okay. Have you ever had experience with other researchers who have been doing cancer studies in mice?

A. I may have. Nothing specific comes to mind. Wasn't -- wasn't a big project that I was working on.

Q. Okay. So I do appreciate that working with laboratory animals is not something that you yourself have done in your career, but do you have an understanding at all as to whether or not -- or as to how common it is to administer the compositions to mice intraperitoneally?

A. I don't know how common it is, no.

Q. Okay. All right. Now, are you familiar with the Animal Welfare Regulations promulgated by the USDA?

A. What do you mean by "familiar"? Just do I know about -- that they exist?

Q. Yes.

A. Yes.

Q. Have you ever had an opportunity to review those regulations?

A. No.

Q. Okay. How about the Policy on Humane Care and Use of Laboratory Animals? Are you familiar with that policy?

A. Using your definition of "familiar," yes.

Q. So you're aware of it?

A. I'm aware of it, correct.

Q. Have you ever had an opportunity to review that particular document?

A. No.

Q. Okay. So let's return for a moment to your report, and I want to return to the claim for one moment, and that's at 42.

A. I'm there.

Q. Okay. Thank you.

When I refer to "the claim," I'm thinking about the claim with the construction the Court has provided. Okay? So in other words, in -- you would substitute pharmaceutical composition with the construction the Court has provided. Okay?

A. Okay.

Q. For clarity. All right.

Now, based on that claim, what, if any, understanding do you have as to whether the pharmaceutical compositions described therein are required to be acceptable for human use?

A. Described therein you mean specifically in the claim?

Q. In the claim, right.

A. Not generally in the patent but in the claim?

Q. Right.

A. My understanding that it's not -- is that it's not limited to human use.

Q. Okay. So it does contemplate pharmaceutically acceptable compositions that could be administered to laboratory animals, for

example, correct?

MS. PIPER: Objection to form.

A. Well, I wouldn't say it that way. I think it's -- can -- it's more inclusive than humans, so it could be used for veterinary purposes.

Q. Okay. All right. So your understanding is, it could be used for humans and veterinary purposes. And what's the basis of that understanding?

A. The basis is the claim. And I understand that there was some discussion with the Court about whether it's limited to humans, and I understand that it's not.

Q. Okay. So based on looking at the claim and that discussion with the Court, it is your understanding at least that the claims do contemplate pharmaceutical compositions for veterinary purposes, right?

A. Yes.

Q. Okay. And that would include animals such as mice, correct?

MS. PIPER: Objection to form.

A. It could if you're trying to treat

mice. I guess if you have a pet mouse, for example.

Q. Okay. So let me -- tell me a little bit about what your understanding -- what you mean when you say "pharmaceutical compositions can be used for veterinary purposes."

A. What I mean is that as a pharmaceutical composition, it's used to treat or to attempt to treat a kind of disease, and so that can be done for humans or for nonhuman animals, the latter being veterinary purposes.

Q. Based on your experience, is it -- strike that.

Now, you'll agree with me that in the context of laboratory research using animals, animals are often being treated for diseases, correct?

MS. PIPER: Objection to form.

A. Well, it depends on the experiment, the laboratory experiment, and the purpose of the experiment.

Q. So there are -- there are specific contexts, you will agree, wherein laboratory animals have disease or some sort of condition

which is being treated in the lab using pharmaceutical compositions, right?

A. As a hypothetical, that's certainly a possibility.

Q. Well, that's an important part of drug research, isn't it --

MS. PIPER: Objection --

Q. -- using laboratory animals to see how a target API is able to treat laboratory animals, correct?

A. That's one part of laboratory research involving animals.

Q. But it's almost unheard of, isn't it, to have -- in the drug application process to actually have a research plan that doesn't involve treating laboratory animals with the API at some level, correct?

MS. PIPER: Objection to form.

A. I'm not quite sure I understand your question. You're talking about filings to regulatory authorities? Or --

Q. So just the -- you know, in the context of pharmaceutical drug development, isn't laboratory research using animals -- it

almost always involves the use of laboratory animals, right?

MS. PIPER: Objection to form.

A. There's quite extensive use of laboratory animals in different stages of, let's say, drug creation, if that's what you mean.

Q. Yes. Okay. And oftentimes that use includes having animals that are used as models of a specific disease, correct? So -- let me strike that.

Are you familiar with the use of xenografts in mice as a model for studying potential candidates for treating cancer?

A. Yes.

Q. And what is a xenograft?

A. A xenograft is when you put in foreign tissue or foreign cells into an animal such as a mouse, laboratory mouse.

Q. So, for example, tumor cells that might have been harvested from a human, correct?

A. That's an example, correct.

Q. Okay. And then -- and so often in xenograft studies, the tumor cells are injected into the mouse and then the tumor is allowed to

grow, correct?

A. That's an example, correct.

Q. Right. And in many contexts if the tumor is left untreated, it will result in the death of the animal; is that correct?

A. Well, I wouldn't quite say it that way. In the type of experiments that you're talking about the objective is not to treat the animal but to perform experiments to -- whatever the -- broadly speaking, the experiment is meant to accomplish. It's not to treat the animal.

Q. That wasn't my question. My question was, when the xenograft tissue is introduced into the animal and the tumor is allowed to grow, if the tumor isn't addressed, it will -- the tumor will grow and result in death of the animal, correct?

A. Well, you are just talking broadly. I mean, I guess it depends on the type of tumor and the type of research that's being done and the hypothesis that's being tested.

Q. Okay. Well, based on your review of the prior art in this case, isn't it true that the xenograft studies that were performed in the

prior art resulted in tumors that left untreated were fatal to the mice?

A. And just to be specific, you're talking about the -- what I call the Boschelli 2001 reference?

Q. That is an example of the prior art, yes, that's correct.

A. Yeah, so in that reference so that is a study performed on laboratory mice in which, as you say correctly, there were xenografts performed on mice that were meant to be sacrificed.

Q. Is it important that they were meant to be sacrificed?

A. Yes.

Q. Why is that important?

A. Because -- and, again, if there's a specific place in that reference, we can talk about the specific place. But in general terms, the objective of Boschelli and coworkers was not to treat laboratory mice per se, but to test a variety of hypotheses and -- and to determine outcomes. And what's important about sacrifice is that either way, if the tumors went away or

if they didn't go away, the mice were not to continue living.

Q. So, in your opinion, is the fact that they weren't intended to continue leaving relevant to whether or not the experiment was a treatment of the animal?

A. Yes. Living -- just to be clear, I think living -- I don't know how it came out. But -- so, yes, because, again, the objective wasn't to treat animals, to cure them from a disease, or to manage a disease. The objective was to do experiments, and they were going to die either way regardless of the outcome.

Q. In your opinion, the fact that they were going to die either way, is that relevant to the types of pharmaceutical excipients one would select for a composition?

A. Yes. Could be, yes.

Q. Why?

A. Well, I've opined in my report, we can go to the specific places, but there are different requirements depending on what you're intending to do with the animals. I have references, for example, of -- Wolff reference,

which we can talk about if you're interested. But I discuss this in many paragraphs in my report.

Q. Okay. So when you say "there are different requirements depending on what you're intending to do with the animals," can you elaborate on that for me a little bit? And, yeah, feel free --

A. Yes.

Q. -- to go to your report and direct me to that specific paragraph.

A. So, for example, on page 21, and subsequent places in my report, starting paragraph 67, that's when I talk about the fact that there's the xenograft done, the mice did not have CML, Compound 31a, which is also bosutinib, was not being administered to provide a therapeutic benefit, and the animals were to be sacrificed after testing.

And I talk -- I mean, essentially, the bulk of the substance of my report is why what was used or not pharmaceutically acceptable compositions or a pharmaceutically acceptable composition.

Q. And that's the heart of your opinion, right? That the composition of Boschelli wasn't a pharmaceutically acceptable composition, correct?

A. That's a major part of, I guess, the conclusion, and -- and I discuss in multiple pages and paragraphs why that's the case.

Q. Now, I understand that you've been engaged as an expert witness in patent litigation cases previously, correct?

A. Yes.

Q. And have you ever been asked to give an opinion about a claim that patent lawyers taught -- defined as a method claim?

A. I'm pretty sure the answer to that is yes. I'm not thinking of one specific claim as we speak, but I'm sure I have.

Q. Based on your experience, is the claim of the '625 patent a method claim?

A. That's a legal question. I really leave that to the lawyers. I mean, my opinion certainly focused on the science and the meaning within the context of the claim construction.

Q. Okay. Does -- do you have any

understanding as to whether or not Claim 1 of the '625 patent requires treating CML with a pharmaceutically acceptable composition?

MS. PIPER: Objection. Outside the scope of what Dr. Trout was asked to opine on.

A. I don't have an opinion on that.

Q. Okay. All right. You did direct us to paragraph 67, so why don't we take a look at that, paragraph 67 of your report. And this is that section of your report wherein you are stating your opinions that the Claim 1 of the '625 patent is not anticipated by Boschelli 2001.

And Boschelli is spelled B-O-S-C-H-E-L-L-I, correct?

A. Well, this is really a -- a summary. I would say my whole report addresses that issue.

Q. Okay. Fair enough.

So at 67 here, you say, "Boschelli 2001 discloses a newly lab-synthesized compound that is tested in animal experiments."

Correct?

A. Yes.
Q. That lab synthesized compound is bosutinib, correct?
A. Yes, the Compound 31a.
Q. Okay. All right. Compound 31a in Boschelli 2001 is bosutinib, right?
A. That's the molecule, yes.
Q. Okay. Next you say, "In those animal studies reported in Boschelli 2001, human CML tumor cells were introduced into laboratory mice, and the tumors were assessed after administration of Compound 31a."
Correct?
A. Yes, that's what I wrote.
Q. Okay. And then you go on to say, "The mice did not have CML."
And so first -- let's just focus on that for a moment. What do you mean when you say, "Mice did not have CML"?
A. What I mean is that the mice were not being treated for CML. They didn't -- they weren't taken to the lab with CML. They were specifically given humor CML tumor cells to be experimented on.

Q. So isn't CML characterized by a tumor, CML that -- the myelogenous tumor cells?
MS. PIPER: Objection to form.
Q. I mean -- I mean, that is what characterized the CML, right, having tumors that are cancerous?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
A. I'll leave it to the medical doctors to answer that question.
Q. So you don't disagree that human CML tumor cells were introduced into the laboratory mice, correct?
A. Correct.
Q. Okay. And that those CML tumor cells were allowed to proliferate in the mice, correct?
A. Well, there were different types of experiments but broadly speaking, I would say the cells were introduced, and the effects of various compounds on those cells were tested, in particular bosutinib.
Q. And -- right. And so bosutinib was administered to these mice after they had -- the

CML tumor cells had been introduced, correct?
Let me direct you to -- perhaps I can direct you to page 46 of your report.
A. So I think that there were two different types of experiments which they call staged and unstaged and --
MS. PIPER: Clarification. Paragraph 46 or page 46?
MR. BENSON: Paragraph 46.
Q. Are you at paragraph 46?
A. Yes.
Q. Okay. All right.
A. So in the experiments discussed at the top of 46, the -- the tumor cells were inoculated first.
Q. And then they were allowed to reach 15 percent of the body weight of the mouse, correct?
A. Well, I mean, that's when -- I guess, as I have written here, that's when the experiment was ended.
Q. Right. Okay.
Well, let me -- and then there was an unstaged model, correct?

A. Yes.
Q. Okay. And then you write here that, "Boschelli 2001 concluded Compound 31a effectively inhibited tumor growth."
Correct?
A. Yes, I'm just quoting from Boschelli.
Q. And you don't disagree with that conclusion, correct?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
A. I don't have an opinion. I'm just quoting -- this is background on Boschelli, and I'm just quoting Boschelli here.
Q. Okay. So you didn't independently assess whether Compound 31 did or did not inhibit tumor growth in this model, correct?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
A. That's correct.
Q. Do you have any reason to disagree with the conclusions of Boschelli?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
A. I don't have any reason to agree or

disagree. I'm just providing quotes of background from Boschelli. I didn't analyze that separately.

MR. BENSON: Okay. Okay. Do you want to take a -- is this a good time for a short break?

THE WITNESS: Sure. If you want to keep going, we can keep going. If you want to take a break --

MR. BENSON: Yeah, I could use a break.

THE VIDEOGRAPHER: The time is 10:14 a.m., and we are going off the record.

(Recess from 10:14 to 10:28.)

THE VIDEOGRAPHER: The time is 10:28 a.m., and we are back on the record.

Q. Okay. All right. Let's return to paragraph 46. And this is, again, just your -- you know, kind of just articulation of what you see in Boschelli, correct?

A. Well, it's part of the background in Boschelli.

Q. Yeah. Okay. All right. Now, so

setting aside for the moment -- so the vehicle we see here that you describe at paragraph 46, I think it's the second -- no, third full sentence, you're quoting, and it says, "The vehicle used was 2 percent TWEEN 80 and 5 percent dextrose/water."

You see that?

A. Yes, that's part of the quote.

Q. Okay. Now, setting aside the pharmaceutical grade of excipients used, you don't disagree that that describes a pharmaceutical vehicle that could be used with an API in the context of -- as that would be described in the invention?

MS. PIPER: Objection to form.

A. I'm sorry, just to be clear, you're asking a hypothetical outside of the Boschelli?

Q. Let me ask a different question. Okay. Now, do you recall in Dr. Lindsley's report he gives the opinion that 3 milligrams of bosutinib, 10 milligrams TWEEN 80, and 25 milligrams of a dextrose/water mixture was placed in a .5 milliliter aqueous vehicle? Do you remember that testimony?

A. Maybe we could go to his report. I remember something like that, but I haven't memorized his report.

MR. BENSON: Do we have a copy of his report?

Here you are.

MS. PIPER: Thank you.

MR. BENSON: I don't know if there are -- Alembic, if there are portions of it that are -- there might be portions of it that address the infringement position with respect to Sun, so you might want to --

MS. WEISBRUCH: And if I need to step outside the room, that's fine, too.

MR. BENSON: No, that's fine. It's just that it might be in the binder so --

MS. BEIS: The report itself was submitted on behalf of both Sun and Alembic so --

MR. BENSON: Yeah, but there might be -- I think there's a section --

MS. BEIS: We will let you know if something comes up.

MR. BENSON: I'm not going to be

directing you to any of those portions.

MS. WEISBRUCH: If I need to step out, just let me know.

MR. BENSON: Sorry, just protective order issues.

Can I have this marked as the Trout Deposition Exhibit Number 2, please.

(Opening expert report of Craig W. Lindsley, Ph.D. and reply expert report of Craig W. Lindsley, Ph.D. were marked Trout Exhibit 2 for identification, as of this date.)

THE WITNESS: Thank you.

MR. BENSON: Okay. Did I hand you a copy, Counsel? I did. Okay. Thank you. Sorry.

MS. PIPER: Thank you.

Q. I've handed you -- the court reporter has handed you what we've marked as Trout Deposition Exhibit Number 2, and this is a binder that contains two documents tabbed 1 and 2. The first is the opening expert report of Dr. Craig Lindsley and the second is the reply expert report of Dr. Lindsley.

Could you please just briefly take a look at those two documents and confirm these are the expert reports of Dr. Lindsley that you have reviewed in connection with your work in this case.

(Witness reviewing document.)

A. Okay. I've flipped through these, they're over a hundred pages, and they look like the two reports that I reviewed.

Q. Okay. Thank you very much.

I will direct you to the first tab, which is the opening report of Dr. Lindsley. And in particular, I would like you to go to -- paragraph 161 and 162 is where we will be.

MS. PIPER: One clarification. This entire binder is Trout Exhibit 2, both reports?

MR. BENSON: Yes.

MS. PIPER: Thank you.

MR. BENSON: You're welcome.

A. Without the exhibits?

Q. That's correct.

A. Okay. I'm at paragraph 161 and 162.

Q. Okay. Now, this is that part of

Dr. Lindsley's report wherein he opines the Claim 1 of the '625 patent is invalidated as anticipated by Boschelli 2001, right?

A. Yes. And that's the heading in the -- the previous page 57, section Roman numeral IX.

Q. And these are the specific opinions you're responding to in your own expert report, correct?

MS. PIPER: Objection to form.

A. I mean, I -- I think -- I'm responding generally -- in general terms to the opinions in his report, or maybe other location, I wouldn't say it's limited. But this is certainly the section in which he opines that the patent is invalid or Claim 1 of the patent is invalid.

Q. Just so -- the avoidance of any ambiguity moving forward, the only opinion of Dr. -- well, Dr. Lindsley has provided a number of opinions about the invalidity of the '625 patent, correct?

A. Yes.

Q. And one of those opinions, speaking in the broadest sense, is that Claim 1 of the '625 patent is anticipated and therefore invalid,

correct?

A. Correct. That's one of Dr. Lindsley's opinions.

Q. And that is the sole opinion to which you are responding to in this case, correct?

A. Yes, that's correct. Specifically anticipation due to the Boschelli 2001 document.

Q. Correct.

A. Correct.

Q. Okay. I just wanted to be sure, any of his other opinions about the '625 patent being invalid for written description, for example, you're not opining on that particular aspect of his report, correct?

A. Correct.

Q. And his opinions about enablement or any section -- well, any of the section 112 arguments he is making in his report, you're not responding to those particular arguments, correct?

A. Counsel, that sounds like a legal term. I'm solely responding to anticipation due to Boschelli 2001.

Q. Okay. All right. Yeah. I think

that's clear. Thank you.

All right. So let's return to paragraph 161, and in this particular paragraph, second sentence, Dr. Lindsley is -- is stating his understanding of Boschelli 2001 as disclosing, "Xenograft studies wherein bosutinib was dosed ip in amounts up to 100 milligrams per kilogram as a 0.5 milliliter solution prepared in 2 percent TWEEN 80, 5 percent dextrose/water."

Do you see that?

A. Yes, I see that written here.

Q. Do you disagree with Dr. Lindsley in that regard?

A. Well, I don't disagree that -- that Boschelli states that. I mean, Boschelli is doing a lot more than just that, and other amounts, too. But there's nothing wrong with that sentence if one understands that it's part of a broader context.

Q. Right. Okay. And then the next -- the next paragraph 162, Dr. Lindsley concludes, "Thus, Boschelli 2001 discloses a composition comprising approximately 3 milligrams bosutinib,

10 milligrams TWEEN 80, and 25 milligrams dextrose/water in a .5 milliliter aqueous vehicle."

Do you see that?

A. Yes. And just to be clear, you -- actually I think the way you said it is probably better because you didn't read the "and enables" so --

Q. Yeah, I didn't want to get -- yeah, I just wanted you to focus on the composition that he describes. Okay?

A. Yes. Okay.

Q. And we'll get back to the enabled part.

But do you disagree with Dr. Lindsley that the composition disclosed in Boschelli is as stated here in paragraph 162?

A. Well, Dr. Lindsley seems to be basing that on certain assumptions and calculations. I -- I didn't try to reproduce those calculations or determine whether his assumptions are valid or not. But I can take what he's written here and discuss it.

Q. Okay. Well, you haven't disagreed

with it in your own responsive report, correct?

MS. PIPER: Objection to form.

A. I -- I don't think that I -- well, I don't remember specifically. I would have to look through my report. But I know I did not reproduce his calculations or attempt to validate his assumptions in my report, or in my activity in this case.

Q. Okay. Do you have any reason, as you sit here today, to disagree with Dr. Lindsley with respect to his conclusions here at paragraph 162 as to the composition components?

A. I don't have a reason to disagree or to agree with his 3 milligrams of bosutinib calculation, except that he seems to take only one of the concentrate -- one of the amounts of dosing used by Boschelli 2001.

Q. Okay.

A. There are others there, too.

Q. Okay. Well, it's fair to say you don't independently come up with your own calculations with respect to the compositions disclosed in Boschelli, correct?

A. That's correct. I did not do my own

calculations.

Q. Okay. And we can agree just for -- just broadly speaking, setting aside whether or not any of the excipients used in Boschelli were pharmaceutical grade excipients, we can agree that Boschelli discloses compositions containing bosutinib, correct?

A. Compositions as such, Boschelli does not call them pharmaceutical compositions. But if you mean compositions broadly, then, yes.

Q. Yes. And those compositions disclosed in Boschelli are compositions containing bosutinib as the API, correct?

A. Well, again, API means active pharmaceutical ingredient. The bosutinib is designated as Compound 31a in Boschelli. And again -- and I elaborate my opinions in my report, but it's not being used as a pharmaceutical here. So I wouldn't use it as an -- I wouldn't characterize it as an API, and I don't think Boschelli does either.

Q. What would you characterize bosutinib in this composition? What is it?

A. It's a -- a chemical that was

synthesized and tested to -- in a series of experiments to determine its effects on various cells and other assays.

Q. Okay. You don't disagree bosutinib is, in fact, an active pharmaceutical ingredient, right?

MS. PIPER: Objection to form.

A. I don't disagree that it is today.

Q. So do you disagree that at the time of Boschelli that bosutinib was an active pharmaceutical ingredient?

A. I -- I don't know if I've specifically opined upon that. I mean, I know that it's not used as a pharmaceutical. Let's put it that way. And -- and to me sitting here and trying to answer your question, an active pharmaceutical ingredient has to have a pharmaceutical effect.

Q. When --

A. I don't think -- and I don't think that's -- the objective was not to have a pharmaceutical effect per se in Boschelli. It was to study the effect of a variety of different synthesized chemicals including 31a,

which we can call bosutinib.

Q. What -- when you say "pharmaceutical effect," what does that mean to you?

A. It means -- or we could use the term "pharmaceutical activity." It means to me that it's used to treat, let's say, patients of whatever sort. I don't mean that it has to be commercialized. It could be earlier than that.

Q. So is it -- is your definition intentional? In other words, when it's being administered, one has to intend it to have a specific effect? Is that what you're suggesting?

A. I don't think I'm suggesting that it's intentional, that it's -- intentionality. I think -- I mean, it depends what you mean. It has to be administered in a certain context, so in that way maybe there's an intentionality in choosing the context.

Q. So the compound described in Boschelli is bosutinib, correct, the Compound 31a? I mean, we've already established that, right?

A. Yes.

Q. All right. And chemically it's the

same bosutinib as is currently marketed in the -- in the drug Bosulif I believe is the -- yeah, Bosulif, correct?

A. Yes, that's my understanding.

Q. Okay. So the identity of the actual chemical entity is -- is no different in Boschelli than it is in the marketed drug Bosulif, right?

MS. PIPER: Objection to form. And also objection. Outside the scope of Dr. Trout's opinion.

A. I mean, it -- again, I'm not sure maybe what you mean by "chemical entity." I think maybe I -- if I understand your question correctly, what I have opined upon is that the 31a as it synthesized and with the impurity levels, and whatnot, is not an API as such, something that would go into a -- a -- a pharmaceutically acceptable composition.

Q. The -- an active pharmaceutical ingredient, so to the -- let me strike that.

To the extent we're talking about bosutinib as an active pharmaceutical ingredient, we're talking about the chemical

compound bosutinib, correct?

A. No, I think we're talking about the compound -- well, there were two different contexts, and maybe we're talking at cross purposes. But active pharmaceutical ingredient, API, uses pharmaceutical, so it seems to me that it's more than just a chemical. There's something more behind it than just that. If you want to define it as such, you know, we can talk about it in those terms.

Q. Did the inventors do -- in this -- in -- did the inventors of the '625 patent do anything to the chemical compound bosutinib that was different than -- or that rendered it to be a pharmaceutical wherein in Boschelli it was not?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. I didn't opine on that question.

Q. So I'm trying to understand, I guess, how bosutinib is a pharmaceutical now but it was not a pharmaceutical in Boschelli. And can you help me understand your opinions in that regard?

A. Yes. For example, we can look at my

report pages 14 and 15, paragraphs 51 and 52, in which a defined active pharmaceutical ingredient, component of a pharmaceutical composition, and -- and it goes on. And I -- I think as a summary, an important part is that the API has to meet certain specifications.

And I should say, there are other parts of my report in which I discuss this. This is one part, right? You can go to the other parts if you want.

Q. All right. So I understand your opinion that -- I understand your opinion that the bosutinib in Boschelli was not pharmaceutically acceptable as you use that term, correct? That's your opinion?

A. My opinion is that it's likely not. It was not characterized as such, and so it's likely not.

Q. Okay. That's fair. Thank you.

But you're -- you're not saying that bosutinib itself doesn't have the very same activity in inhibiting, for example, Src kinase, tyrosine kinase, as it does in the marketed product Bosulif, right?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. I haven't opined on the activity of this drug per se, or the activity of a compound, or -- or whatnot.

Q. You don't disagree that Boschelli concluded by administering the composition that contained bosutinib, they were able to inhibit tumor growth in the mice they studied, right?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. I think, as we discussed, I quoted Boschelli in background, for example, paragraph 46. I didn't independently analyze that.

Q. But you are testifying today that the bosutinib in Boschelli is not a pharmaceutical; is that right?

MS. PIPER: Objection to form.

A. It's -- it's -- well, it's not a pharmaceutical composition.

Q. Okay. So the -- the composition which included bosutinib, TWEEN 80, dextrose, and water, your opinion is, that is not a pharmaceutical composition; is that right?

(Witness reviewing document.)

A. I -- I think a better way of saying is what -- what I opined is, for example, on page 25, paragraph 77, "There is no indication in Boschelli 2001 of pH control in the disclosed TWEEN 80, dextrose/water solution," that's one aspect. And I talk about various, let's say, lacks of indication. So there's no indication that what we are discussing is a pharmaceutical composition and for a variety of reasons.

Q. Okay. The question I have then is, as you sit here today, is it your opinion that the Boschelli composition is not a pharmaceutical composition?

A. My opinion -- and, again, there's a lot in my report that gets here -- is that there's no indication that it discloses a pharmaceutical composition for -- for a variety of reasons that I mention here.

Q. Does the fact that the composition was administered ip to mice for the purposes of inhibiting tumor cell growth any indication to you as to whether or not it was a pharmaceutical composition?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. I don't think I have in my report an opinion about that.

Q. Okay. So if -- if the -- if the -- can we just agree that whether it's a pharmaceutical composition or not, that Boschelli, in fact, discloses a composition, correct?

A. Yes, we can call it a composition.

Q. Okay. So the composition of Boschelli, had they included purity information as to the bosutinib, would that change your opinion as to whether or not the composition of Boschelli was a pharmaceutical composition?

A. So it depends on the details of this hypothetical. I mean, I would have to go through what their disclosure would be. I mean, there's -- that's not the sole reason. I have a whole variety of reasons which led me to this opinion.

Q. Okay. So one of the other reasons, in your opinion, was that there was no indication in Boschelli that the excipients used were

pharmaceutical grade, correct?

A. That's correct.

Q. So --

A. If -- just to be clear, that's another -- there's a variety.

Q. Yeah. So let's say a hypothetical that Boschelli disclosed that the bosutinib was pure and that the excipients used were pharmaceutical grade excipients. Would that then change your opinion as to whether or not Boschelli disclosed a pharmaceutical composition?

A. Well, I would need to -- certainly that would affect -- if the excipients were disclosed as pharmaceutically acceptable, that would certainly affect my analysis. I'm not sure what "purity" means in -- in the context of your question. I mean --

Q. Well, one of the issues you took with the bosutinib was that it hadn't been purified to the degree one would expect of a -- an API that is going to be incorporated in a drug for use in treating patients, right?

A. Yes. Purity is a -- was a significant

issue, for example, on my paragraph 70.

Q. Okay. So let's say that the bosutinib was pure, and the excipients used in the Boschelli composition were pharmaceutical grade excipients. Now, with that information, would your opinion change as to whether or not the composition of Boschelli is a pharmaceutical composition?

A. And, Counsel, I'm not trying to split hairs but it's -- I think saying that a compound is pure is a little more complicated. So it has to be characterized and the -- the impurity profile needs to be characterized. If you're telling me that it was characterized and there was no detectable impurities, then that would -- I would have -- have to redo my analysis --

Q. Okay.

A. -- based on that.

Q. Okay.

A. It would be very unusual if that were the case.

Q. Well, let's say that is the case. Let's say it is pure bosutinib, and the excipients in the formulation were

pharmaceutical grade excipients. With that hypothetical, how would that change your opinion as to whether or not the composition in Boschelli was a pharmaceutical composition?

MS. PIPER: Objection to form.

A. I would have to go through -- I mean, I list a whole variety of other issues. But that would change my set of opinions in the sense that those two opinions, again, with purity being -- it was characterized in an adequate way for a pharmaceutical, I would have to take that into account in a reanalysis.

Q. Okay. But you haven't -- you haven't considered that in -- as you sit here today, you haven't considered that -- how those factors would change your opinion. Is that fair?

A. Well, I've considered them broadly in the sense that I considered what was necessary for something to be a pharmaceutical composition and what the disclosure in Boschelli 2001 was. So I considered them in that broad sense. I didn't do an -- before today do an exercise in the specific hypothetical.

Q. So you'll agree with me Boschelli

doesn't disclose -- well, strike that.

You'll agree with me the excipients used in the Boschelli experiments weren't identified as non-pharmaceutical grade excipients, right?

MS. PIPER: Objection to form.

A. That's right. They -- their source was not identified at all. And so they weren't explicitly identified as non-pharmaceutical versions. But I think the skilled person would expect that if they were pharmaceutical compositions, that would be disclosed.

Q. Why is that?

A. Because it means that there was a -- a specific grade that was used, and there was -- there would be specific attention paid to that. The researchers in Boschelli did not pay specific attention to the type of -- call them excipients used.

Q. Are you saying they didn't pay attention to it, or they simply didn't disclose it in their paper?

A. Well, I mean, pay attention to it in the sense of bringing attention to it, let's

say, disclosing it to the reader of this paper, if you want to say it that way.

Q. But wouldn't a person of ordinary skill in the art who is familiar with animal studies expect that the excipients were pharmaceutical grade excipients?

MS. PIPER: Objection to form.

A. I think I've given a variety of opinions in which person, let's say, would not necessarily expect from the disclosure in Boschelli, and specifically, there's a reference from an author named Wolff which talks about the fact that they could very well be non-pharmaceutical grade.

Q. But doesn't Wolff disclose that the default is that it -- that excipients should be pharmaceutical grade excipients, absent some extenuating circumstances?

MS. PIPER: Objection to form.

Q. And if you would like to go to Wolff, we can do that.

A. Yes, that would be great.

Q. Let's go to -- this is going to be Exhibit T, as in Tom, in your report.

And -- you have that?
A. Yes, I'm there.
Q. Okay. Is this the Wolff reference you're referring to?
A. Yes.
Q. Okay. All right. And I believe the specific section you were addressing is on -- if you look at the bottom left-hand corner of the Wolff reference, there is a page number. And I'm looking at page 34. Are you there?
A. Yes.
Q. And your opinion focuses on the question in the middle column of Wolff. It's the third question, and it states, "Are the scientists at our institution allowed to use non-pharmaceutical grade chemical compounds in physiological preparations involving laboratory animals?"
Right? That's the question?
A. Yes. And then there's another sentence after that but that's --
Q. Okay. And then it -- right. So let's focus on that part of it first. And so it's your opinion that Wolff -- and I think the part

that you focused on is that Wolff recognized that under certain circumstances the use of non-pharmaceutical grade excipients is allowed, right?
A. Well, I mean, the second sentence in the query is probably important because it also differentiates survival versus non-survival experiments. But the way Wolff answers it in his first sentence that you're referring to, alluding to that it's allowed but specifically saying, "It's a necessary and acceptable component of biomedical research."
Q. Okay. So -- but doesn't -- but Wolff goes on to say that, "The use of non-pharmaceutical grade excipients should be based on, 1, scientific necessity, 2, nonavailability of an acceptable veterinary or human pharmaceutical grade compound, and, 3, specific review and approval by the IACUC."
Correct?
A. Yes.
Q. All right. Now, do you see anything in Boschelli that would lead you to believe that there was a scientific necessity to use

non-pharmaceutical grade TWEEN 80 and dextrose?
A. Well, I would say it the other way around. There was not a scientific necessity for Boschelli to use pharmaceutical grade compounds. So I think that's the way I would address Number 1 here.
Q. Isn't -- I mean, when scientists are doing research involving laboratory animals, isn't the fact that these are living creatures reason enough in a scientific justification for using pharmaceutical grade excipients in things being administered to those animals?
A. No. I think that's exactly the point of the Wolff reference. Again, these animals were specifically induced with cancer with the intention of studying the effect of chemical -- chemicals on cancer, with the intention that no matter what they were to be sacrificed.
Q. So under those circumstances it didn't matter whether it was pharmaceutical grade excipients. Is that your testimony?
A. My testimony is that there's no indication that pharmaceutical excipients were used, and there was not a necessity that

pharmaceutically acceptable excipients were used. And, again, that's just part of my opinion. The composition and the chemical itself are other parts of it. But if we're just focused on the excipients...
Q. But here the use of non-pharmaceutical excipients has to be based on scientific necessity, not the use of pharmaceutical excipients, correct?
MS. PIPER: Objection to form.
A. Well, I mean, my reading of it is, is it necessary to use non-pharmaceutical? Is it necessary to use pharmaceutical? One would -- I think you have to look at this in a broader -- in the broad way in which the authors Wolff, et al., are trying to address this.
Q. Did you talk to any of your colleagues who do scient -- who do animal research to determine what their standard practice would be with respect to the use of pharmaceutical versus non-pharmaceutical grade excipients?
A. No.
Q. Okay. Well --
A. And I mean, just to be clear,

specifically in this case and specifically in that way.

Q. Right.

A. I've certainly talked to colleagues outside of this case and before about animal studies and what they use.

Q. You've had discussions about that specific issue, about whether they use pharmaceutical grade or non-pharmaceutical grade excipients in compositions they're administering to animals?

A. I have not specifically posed that question. I just had general discussions.

Q. Okay. So what is the basis of your understanding that a person of ordinary skill in the art reading Boschelli would not understand the excipients to be pharmaceutical grade excipients?

A. Again, my opinion is that there's not an indication that they're pharmaceutical grade excipients, and that's based on -- I mean, there's a variety of reasons in my report. But if you want me just to summarize, I mean, I would take my opinions as a whole in the report.

But a couple of those opinions are that there's no specific disclosure that they're pharmaceutical grade. Also, there's no scientific necessity because these are experiments that are done early on in the discovery phase in which the animals are induced with the cancer and meant to be sacrificed.

Q. Okay. So this idea that the animals are meant to be sacrificed, can you just explain -- and I know that you've -- you've talked generally about that, but how is that important for your opinion that the Boschelli composition was not a pharmaceutical composition?

A. Because the animals are not being treated per se to cure a disease. They're being studied for the effects of various compounds and -- in various assays including the xenograft study. And so the idea is not to treat them. The idea is to study and then sacrifice them regardless of the outcome. So -- yeah, stop there.

Q. Okay. So one -- one -- so the fact that they're going to be sacrificed leads you to

believe that they're not being treated, correct?

I mean, that's one opinion you have?

A. I think that's an important component.

Q. Okay. And then anything else? Any other relevance to the fact that these are -- animals are going to be sacrificed? How does that affect any of your other opinions about the composition in Boschelli?

A. Well, again, my conclusions are based on my analysis as a whole, and that's really the entirety of the substance of my report. So it's all -- it's all part of analysis of the full disclosure in Boschelli.

Q. Okay.

A. So that full disclosure including the fact that they were not going to survive, they were going to be sacrificed, leads me to the conclusion that I had.

Q. Would that lead a person of ordinary skill in the art, the fact that they were going to be sacrificed, to believe the excipients used were not pharmaceutical grade excipients?

A. Again, I'm -- I'm saying that that is another indication. There's no disclosure that

they are. And if you look at the totality of the context of the experiments, including the fact that they were to be sacrificed, and that's an important element, but that's -- that is one element of a set of disclosures which leads to my opinion that there's -- and conclusion that there's no indication that these are pharmaceutically acceptable excipients.

Q. Okay. Now, you don't disagree with me that pharmaceutical grade TWEEN 80 is readily available and would have been at the time of the invention, correct?

A. Well, available, it depends what you mean by "ready." One --

Q. It can be purchased?

A. -- it could have been -- could have obtained it. I'm not sure if there would have been delays or what the supply chain would be, but it was obtainable.

Q. Yeah. You could have bought it from Sigma, right, pharmaceutical grade TWEEN 80?

A. Yes, I think that's one possibility.

Q. Okay.

A. Assuming it was in stock.

Q. And one could have also purchased pharmaceutical grade dextrose from Sigma at the time as well, correct?

A. Yes, I think that's correct.

Q. And one could have easily obtained purified water, correct?

A. Well, again, water, as I've talked, it's not just a matter of purified. It has to be purified and meet certain criteria to be acceptable in a pharmaceutical composition.

Q. But don't laboratories typically -- laboratories that are dealing with pharmaceutical compositions, don't they typically have water purification devices in the laboratories that essentially filter water to create sterile, pure water?

A. Well, I think that's the intention behind, you know, a typical water, let's say, filtration device. I have one in my lab. But I have not specifically analyzed or even used it, tested it to see if it meets some set of standards that would make it pharmaceutically acceptable.

Q. Do laboratories buy pharmaceutically

acceptable water from Sigma, for example?

A. I'm not sure if Sigma is a supplier, but there are suppliers that one could buy it from.

Q. In your experience do labs buy pharmaceutical grade water, or do they create it in their lab using their own filtration devices?

A. I'm not sure how they -- there are various routes of obtaining it. I'm not sure what's most prevalent.

Q. Okay. And the filtration device you have in your lab, explain to me what -- what is the purpose of that specific device?

A. The purpose is to filter and treat water. My lab is in Cambridge, Massachusetts. They have a certain degree, certain criteria for water. We filter it to try to remove impurities that we don't want in the water that, you know, the City of Cambridge, whoever produces their water, leaves in it.

Q. Would a person of ordinary skill in the art have expected the composition in Boschelli was comprised of water that had been filtered in the same way that you filter water

in your lab?

A. I'm not sure. There's no indication that it was -- how it was obtained.

Q. But the question is, would a person of ordinary skill in the art reading Boschelli have that expectation, that that's the type of water filtration -- that's the type of water that would have been used in the composition?

A. I think it's possible, maybe likely, but not certain. I mean, I think it would have to be disclosed for someone to be certain about that.

Q. Okay. So there's no absolute certainty that that is what was used in the composition of Boschelli, right?

A. Well, I didn't say absolute certainty. I mean, what is absolutely certain? I -- I said certainty.

Q. Okay.

A. I said it's possible, but it's also possible not.

Q. How about the -- from the perspective of a person of ordinary skill in the art reading Boschelli, would their expectation have been

that the TWEEN 80 was pharmaceutical grade? TWEEN 80?

A. I think I address this, for example, in my paragraph 74 in which I say, specifically referring to the previous sentence, "Nothing in Boschelli 2001 suggests that the inactive components," including TWEEN 80 in your question, dot dot dot, "in the formulation administered to the laboratory mice were pharmaceutical grade or would have been pharmaceutically acceptable as used." And there's some references.

Q. Okay. I appreciate that. My question was different. Which is, namely, a person of ordinary skill in the art reading -- well, before we get to there, let's agree on one thing.

We can both agree Boschelli is silent as to whether the TWEEN 80 or -- well, let's start with TWEEN 80, is silent as to whether the TWEEN 80 used in the composition of Boschelli was pharmaceutical grade or non-pharmaceutical grade, correct?

MS. PIPER: Objection to form.

A. Correct in the sense there's no specific disclosure of the source or the grade of TWEEN 80.

Q. Okay. And Boschelli is similarly silent as to whether the dextrose used in the compositions of Boschelli was pharmaceutical grade versus non-pharmaceutical grade, correct?

A. That's correct in the sense that there's no specific disclosure as to the source or the -- or the type of dextrose.

Q. Okay. So with that understanding, my question is a little bit different then. It is, a person of ordinary skill in the art reading Boschelli, what would their expectation have been based on their own knowledge and experience as to whether or not the TWEEN 80 was pharmaceutical grade?

A. Yes and -- maybe I don't understand, if -- to the extent I understand your question, and I emphasize maybe this helps, all the opinions in my report are based on the point of view of a person of ordinary skill in the art as I've defined it, or -- you know, there's two different definitions. Either one the opinions

don't change.

And that's why I wanted to stick to specifically what I wrote here in the text suggests that the inactive components, including TWEEN 80 -- there's nothing that suggests that they were pharmaceutical grade or would have been pharmaceutically acceptable as used; definitely from the point of view of the person of ordinary skill in the art.

Q. Well, is there anything about a person of ordinary skill in the art's just experience that would have led them to believe that the pharmaceutical excipients used in Boschelli were, in fact, pharmaceutical grade excipients?

MS. PIPER: Objection to form.

A. I -- I think -- if you mean some degree of certainty, I think -- I mean, I would stick to the words the way I used it in my report, because I know this is a key question in the case, but there's no indication that these are pharmaceutically acceptable or pharmaceutical grade, and so I don't think the skilled person would have had certainty that they are pharmaceutical grade if -- if there's

no indication.

And, again, it's also based on the type of study and the context, and sort of the overall disclosure in the document, too.

Q. Including the fact that the animals were to be sacrificed, right?

A. Yes, that's part of it, including the -- but also the general context of the study which is really in the phases of drug discovery.

Q. The -- well, would a person of ordinary skill in the art reading Boschelli believe it was more likely than not that the TWEEN 80 used was pharmaceutical grade?

MS. PIPER: Objection to form.

A. And just to be clear, this sounds to me like a legal term. Are you asking more likely than not as --

Q. No, it's not.

A. Not. Okay. So not a legal term.

I think my opinion is that the skilled person would understand that there's no indication. I'm not sure what the likelihood would be in a percentage or even qualitative way. I would stick to the terms that I used in

my report.

Q. So if a person of ordinary skill in the art was experienced in doing animal studies and based on that experience understood that pharmaceutical grade excipients should be used, how would that -- wouldn't that influence their expectation about whether the TWEEN 80, for example, used in the composition of Boschelli was pharmaceutical grade?

MS. PIPER: Objection to form.

A. Well, I -- I think I put that -- I took into account that possibility in -- in my analysis, and included a lot of, you know, references and a lot of analyses to achieve my -- or to, you know, come up with my opinions, obtain my opinions.

MR. BENSON: Let me mark something here. Could we mark this as Trout Deposition Exhibit Number 3.

(Guide for the Care and Use of Laboratory Animals was marked Trout Exhibit 3 for identification, as of this date.)

THE WITNESS: Thank you.

Q. Now, so I've handed you a document we

have marked as Trout Exhibit Number 3, and it is the Guide for the Care and Use of Laboratory Animals. Are you familiar with this document?

A. No. I'm familiar with the concept but not this particular document.

Q. And when you say you're "familiar with the concept," what do you mean by that?

A. Well, that such guides exist, we talked about that earlier this morning, and the various criteria.

Q. Okay. All right. So I would like to direct you to page -- looks like my page numbers are behind the clip here. Let me see. I believe it is page 32 of the document. Do you see the page numbers are at the corner?

A. I see the pages.

Q. Okay. It's actually page 31 of the document.

Okay. So are you at page 31?

A. Yes.

Q. Okay. So let's go to that section, it's italicized, and it is -- it is titled Use of Non-pharmaceutical Grade Chemicals and Other Substances. Okay. Now, take a moment to just

read that paragraph there on page 31, and let me know when you're done.

(Witness reviewing document.)

A. Okay. I've read this.

Q. Okay. Now, according to this document it states that, "The use of pharmaceutical grade chemicals and other substances ensures that toxic or unwanted side effects are not introduced into studies conducted with experimental animals."

Do you agree with that statement?

A. Counsel, that's what's written there and you read that, I think, accurately. I haven't seen this document before. It's over a hundred pages. It's got -- I don't know how many references, maybe a hundred references or so. So I would have to analyze this whole document to opine on a -- a specific statement as such.

I don't even know the -- the chapter, heading, or other statements in the document. So I -- I can't sitting here, just now having read that one paragraph --

Q. Sure. We can --

A. -- come up with a conclusion on that sentence.

Q. I'm sorry. I didn't mean to talk over you.

We can agree that the use of non-pharmaceutical grade chemicals and other substances -- that's exactly what we've been talking about for the last 35, 40 minutes, right?

A. Well, I think what we've been talking about is whether the disclosure in Boschelli 2001 is such that the skilled person would understand are pharmaceutical grade, and so I have opined it's not indicated and so it's uncertain. And so I think that's what we have been talking about.

Q. I get that it's uncertain, and I understand that. What I've been trying to get to is what would -- notwithstanding that it is not disclosed in Boschelli, what would a person of ordinary skill in the art have expected. And wouldn't you agree based on -- that this particular document on page 31, that -- the paragraph you just read, that the recommendation

here is that pharmaceutical grade excipients should be used when available for all animal-related procedures, right?

MS. PIPER: Objection to form. And plaintiffs object to the use of the document not considered by Dr. Trout in his report.

A. I see that's what's written in the second sentence in that paragraph.

Q. Yeah. It's written that pharmaceutical grade excipients when available should be used, right?

A. Well, I think it's important to -- you read the whole sentence accurately before. I think it's important to take the whole sentence into account, including the unwanted side effects, and -- and other aspects. And so the foc -- and then that's what the "they" refers to, correct, the pharmaceutical grade chemicals and other substances.

Q. Right. And then there's a citation here to USDA 1997b. Do you have any understanding as to what that reference is to?

(Witness reviewing document.)

MS. PIPER: Again, objection. Dr. Trout has not considered this document in forming his opinion and is not familiar with the document.

A. I'm trying to look up the reference, but it looks like in the back there are all kinds of different sections, and it's not readily evident where that reference is. But I don't --

Q. Okay.

A. -- I don't think it's part of my materials considered.

Q. Okay. Fair enough.

A. Unless I -- unless I'm missing it. We could check the list.

Q. Okay.

A. I don't --

Q. All right. So the next sentence here says, "The use of non-pharmaceutical grade chemicals or substances should be described and justified in the animal use protocol and be approved by the IACUC."

And the citation here is to Wolff, which is the same article you rely upon in your

expert report, correct?

A. And just to clarify -- I'll answer that and to clarify the previous answer, I did find now that -- it's actually -- the references I think are at the end of the chapter, and maybe located in a different place in the end of the whole document, but -- so I see now the Wolff reference there.

(Witness reviewing document.)

A. And, yes, this looks to be the same reference that is my Exhibit T.

Q. And then the USDA 1997b reference is also indicated there, correct?

A. Yes. I see that now in the -- in the list of references at the end of the chapter, whatever, or section, whatever it is.

Q. And that reference is to the APHIS Policy Number 3, quote, Veterinary Care, July 17. Do you see that?

A. Yes, I see that.

Q. Do you know what APHIS stands for?

A. No. But it's probably written in this document somewhere.

Q. Okay. All right. And based on the

date of this, do you understand that this would have been the -- the recommendation that they're referring to here that pharmaceutical grade chemicals or substances should be used when available is a policy that had been promulgated at least as early as 1997?

MS. PIPER: Objection to form.

A. I have not reviewed that -- the reference, the USDA 1997b reference, so I'm not sure if this is an accurate characterization. And I haven't reviewed this document either, except for that one paragraph, so I don't know.

Q. Okay. All right. So this document, though, does -- it does cite the Wolff reference that you've relied upon in your -- in your expert report, correct?

A. Yes.

Q. And what it says about Wolff is that the use of non-pharmaceutical grade chemicals or substances should be described and justified in the animal use protocol and be approved by AUCUC, right?

A. IACUC, yes.

Q. I apologize.

A. IACUC. Yes. That's what's written here.

Q. So wouldn't a person of ordinary skill in the art expect that if -- that if non-pharmaceutical grade chemicals were used, that that would be disclosed in the study protocol?

MS. PIPER: Objection to form.

A. Again, I'm looking at one sentence and one paragraph, and that's all I've read in this hundred-page document with lots and lots of references. But I'm -- I'm not -- I don't think that Boschelli is disclosing a protocol per se. Part of a protocol or maybe that is the disclosure of the protocol. But I'm not, frankly, sure exactly what this sentence refers to, so I would really have to study this whole document in detail.

Q. But wouldn't you agree with me that based on the information in this document, a person of ordinary skill in the art would first expect that pharmaceutical grade excipients would be used in animal studies when those excipients are available?

MS. PIPER: Objection. Dr. Trout has not had a chance no review this document and has not considered it in forming his opinion.

A. I'm not sure if that's what the document concludes or even indicates, particularly in the context of the Boschelli 2001 article.

Q. Okay. Well, wouldn't a person of ordinary skill in the art have understood that if non-pharmaceutical grade chemicals or substances were used, that that should be disclosed in the study protocol?

MS. PIPER: Objection. Dr. Trout has not had a chance to review this document and has not considered it in forming his opinion.

A. I mean, again, I read the sentence as such. I'm not sure of the broader context. And I think one would have to understand the -- the document as a whole to interpret what a given sentence and given paragraph and given chapter means.

Q. Well, the context as a whole is Wolff,

right? Because that's what Wolff says, right?

A. No --

Q. If we go back to Wolff, it says: Specific review and approval by IACUC has to be -- has to be achieved for the use of non-pharmaceutical grade excipients.

Right?

MS. PIPER: Objection to form. And Dr. Trout has not had a chance to review this document.

MR. BENSON: I just read from Wolff, and he reviewed it and discussed it at length.

Q. Isn't it true that Wolff explicitly states that, when using non-pharmaceutical grade excipients, specific review and approval by the IACUC must be obtained?

A. Well, going back to Wolff, I mean, that's one of three possibilities in -- in this list from Query 3 in the middle column on page 34. He discussed that there are other possibilities. And, again, these -- these are under a broader statement in Wolff.

Q. Now, the very last -- one of the

sentences in Wolff that, you know -- in that first question, the second part of that that you noted was, it states: Please clarify whether this -- and "this" is the use of non-pharmaceutical grade excipients -- is an allowable practice and whether it makes a difference if the compounds are used in survival versus non-survival experiments.

Right?

A. Yes, that's what's written there.

Q. What does Wolff say about that?

Well, let me ask a different question. Isn't it true that Wolff says that notwithstanding the use of non-pharmaceutical -- of pharmaceutical grade excipients -- let me rephrase that.

Isn't it true that Wolff states that it doesn't matter whether the studies are non-survival studies, the scientific principles requiring the use of pharmaceutical grade excipients is -- still remain the same?

A. You know, I think you're referring to the next to the last sentence in the bottom. It doesn't quite say it the way you stated. It

really says, "Although the potential animal welfare consequences of complications are less evident in non-survival studies, the scientific issues remain the same."

That's what he says.

Q. Right. And the scientific issue is that, all things being equal, if the pharmaceutical grade excipients is available, that's what should be used. Isn't that what Wolff is saying?

MS. PIPER: Objection to form.

A. I don't think Wolff says that.

Q. Well, it says, Under certain circumstances one could use non-pharmaceutical grade excipients. Isn't it true that a person of ordinary skill in the art reading that would say, generally you have to use pharmaceutical grade excipients, under these circumstances outlined here it may be justifiable to use non-pharmaceutical grade excipients?

A. Well, that's correct. But the -- the circumstances of Boschelli, because -- Boschelli 2001 are different, let's say, than other circumstances.

Q. In what way?
A. So -- okay. Just to clarify, and then I'll segue to your question. So Wolff is talking about a variety of different circumstances. And -- and so -- and getting to your question, the circumstances around Boschelli are that the animal experiments are done on mice, and they're done early on in the discovery, as opposed to animal experiments that are done later, like, under preclinical context. And so -- so I think one has to take into account those circumstances in understanding the answer here in Query 3 in Wolff.
Q. What's the justification for using non-pharmaceutical grade excipients when you're administering something to a living animal?
Let me ask a different question. Don't researchers working with laboratory animals have a duty to ensure that the research they're doing causes the least possible harm to the animal?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
A. I'm not sure if they have that duty or

not. I don't have an opinion on that.
Q. I mean, isn't that what the, you know, Guideline for the Use and Care of Animals is all about is protecting animals used in laboratory research?
MS. PIPER: Objection. Again, Dr. Trout has not had a chance to review the entire Guideline for the Care and Use of Laboratory Animals.
Q. You can answer the question.
A. I -- I don't know. I'm not sure -- I haven't read the whole -- and studied this whole document.
Q. Research laboratories are required to have a veterinarian on staff, right?
MS. PIPER: Objection. Outside the scope of the Dr. Trout's opinion.
A. I mean, I'm not sure what you mean. Not all research laboratories. Maybe some.
Q. Do you have any understanding as to what are the requirements for providing veterinary care to laboratory animals?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. I don't have an opinion on that.
Q. Would it change your -- you testified earlier today that the pharmaceutical compositions of the '625 patent are compositions that are appropriate for human or veterinary use, right?
A. In Claim 1 of the '625, yes, it's my understanding.
Q. And if -- if laboratory animals are under the care of veterinarians who are overseeing the medicines being administered to animals, isn't that veterinary care?
MS. PIPER: Objection to form. And objection. Outside the scope of Dr. Trout's opinion.
A. I don't have an opinion on that matter.
Q. Okay. Would it change your opinion if the animals in this particular study were -- were under the care of a veterinarian and the procedures were being overseen by a veterinarian?
A. I mean, I would have to -- I would take that into account. There's no disclosure

in Boschelli as such. So I'm not sure, sitting here, how that hypothetical would change my opinions or not.
Q. Okay. You don't disagree the intent of administering the composition of Boschelli was to inhibit tumor growth in the laboratory mice, right?
MS. PIPER: Objection. Outside the form -- scratch that. Objection. Outside the scope of Dr. Trout's opinion.
A. I don't think I opined upon the intention as such.
Q. You said that the animals weren't being treated; is that right?
A. I believe that's what I said. I may have said more and qualified that. But I think what I said is they're not -- stick maybe to what -- my original answer, but they're not intended to be treated to cure disease. They're intended to test different hypotheses, and -- and in the end to be sacrificed.
Q. How does that matter to an anticipation argument on a claim that doesn't require or include a limitation that is a method

of treating --
MS. PIPER: Objection to form. And --
Q. -- an animal?
I mean, the claim doesn't say -- let me -- you know, let me ask it in a different way, and namely first by directing you to the claim at issue. You can go back to -- I believe it was at paragraph 40 --
A. 42.
Q. 42. Thank you.
The claim itself is just, "A pharmaceutical composition comprising a CML inhibiting amount of bosutinib."
Right?
MS. PIPER: Objection to form.
A. I think that's what it says, yes, pharmaceutical composition --
Q. So the only issue is, is the composition in Boschelli a pharmaceutical composition, right?
MS. PIPER: Objection to form.
Q. That's one issue, correct?
A. Yes, that's the -- the major issue that I opined upon.

Q. And the second issue, is the amount of bosutinib a CML inhibiting amount?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
Q. Right?
A. That's part of the claim, and I didn't opine upon the CML inhibiting amount.
Q. Okay. So your entire opinion is based solely on whether it's a pharmaceutical composition, correct?
A. It being the -- what's disclosed in the Boschelli 2001. That was the focus of my opinions.
Q. Okay. So I'll ask that again in a better way, and you're right. So your opinion is focused solely on whether or not the composition of Boschelli is a pharmaceutical composition as that term has been construed by the Court in this case, correct?
A. Well, that's correct in specifically responding to Dr. -- some of Dr. Lindsley's opinions in that regard, but that's the focus of my report, though.
Q. And just for clarity, you do not give

an opinion as to whether or not the bosutinib in the Boschelli composition is a CML inhibiting amount of bosutinib, correct?
A. That's correct. I do not have -- did not express opinions about CML inhibiting amounts.
Q. Okay. All right. Now, so given your opinion as focused solely on the pharmaceutical composition, I do want to return to paragraph 29, which includes the Court's construction. And I just want to recapitulate where we are in agreement on pharmaceutical composition, specifically looking with reference to the Court's construction. Okay?
MS. PIPER: Objection to form.
MR. BENSON: That wasn't a question.
Q. Okay. So the Court's construction --
MR. BENSON: I'll give you a minute.
MS. PIPER: Sorry.
MR. BENSON: That's quite all right. Those are unwieldy binders.
MS. PIPER: Okay. Thanks.
MR. BENSON: You're welcome.
Q. Okay. So, again, the Court's

construction is, "A pharmaceutically acceptable composition containing the specified compound," in this case bosutinib, "and one or more excipients."
Right?
A. Yes.
Q. Okay. We agree the composition of Boschelli includes -- contains bosutinib, which is under the Court's construction the specified compound, right?
MS. PIPER: Objection to form.
A. Well, I think -- if you're talking about a -- a chemical structure per se, which is somewhat abstract, that's there. But, again, that's a -- whether it's an API and the -- the way it was made in Boschelli 2001 and the way it was characterized, those are central aspects to my opinions in this case.
Q. Okay. I'll ask it again. I think my question was a little bit cleaner. Namely, the composition of Boschelli contained bosutinib, right?
A. Again, I -- it would just stick to my answer. I think it's the same question, which

is that if you're just talking abstractly about the molecule, the chemical formula, that's what is characterized as 31a in Boschelli 2001.

But if you're talking about impurity profiles, acceptability as an API, and those aspects, which I think are important aspects of -- of what goes into a composition, then I express a large number of opinions about that.

Q. I understand, but that's not my question. My question is very simple. It's a yes or no. Does the composition of Boschelli contain bosutinib?

A. And in your -- just to clarify in your yes-or-no question, by "bosutinib," you mean abstractly this chemical formula, which is an abstraction of what a -- a chemical is, or do you mean bosutinib as would go into a pharmaceutical composition, or something else?

Q. I don't think -- I don't think the chemical formula of bosutinib is an abstract in any way, shape, or form, is it?

MS. PIPER: Objection to form.

Q. I mean, that confuses me.

A. In my view as a chemist, a chemical

formula is an abstraction of what's there. It's maybe a model or an indication.

Q. It's a precise definition of what the chemical entity is, right?

I mean, that's how you know what it is. A chemist can read a chemical formula and know exactly what it is, right?

MS. PIPER: Objection.

Q. It knows how many carbons, how many nitrogens, how many hydrogens, how many oxygens, right?

A. Yes, it allows you to count those.

Q. Yeah, and the way that the -- the way that the chemical formula is constructed, it also gives the chemist information as to how those various atoms are connected to one another, right?

A. That's what a two-dimensional chemical representation does, yes.

Q. Okay. So the question is -- and we've already agreed that that chemical formula in Claim 1 is bosutinib, right?

A. Bosutinib the molecule, yes.

Q. That's right. That's what's stated

there. And that's what the claim is all about, does it have that molecule? That's the compound, right?

MS. PIPER: Objection to form.

Q. That's what the claim is about, it's about the compound bosutinib?

A. It's not all about that, Counselor, no. It's about other -- there are other elements, too.

Q. Well, let's go back to the claim. The claim says, "A pharmaceutical composition comprising a CML inhibiting amount of the compound," and then it names the chemical formula which is bosutinib, right?

A. Right, as the chemical.

Q. That's the chemical, right. That's what I'm asking. That's bosutinib. That's what the claim is all about. It's not about an abstraction. It's not about whether or not it was pure or how it -- whether the column chromatography was done, you know, properly or -- it doesn't matter. The question I have is, does the composition of Boschelli contain bosutinib?

MS. PIPER: Objection to form.

A. Well, in -- qualify in my opinion in reading this as a chemist, there -- there are other parts like pharmaceutical composition. But --

Q. I'm not asking about those. I just want a yes or no. Does the composition of Boschelli contain bosutinib? Yes or no?

A. It contains that molecule --

Q. Thank you.

A. -- 31a, as I've testified to. 31a.

Q. Which is bosutinib, correct?

MS. PIPER: Objection to form.

A. It's the bosutinib chemical, if we talk about it, that -- if that's the focus of it, it's -- but --

Q. Let me do it a different way.

A. Just to finish my answer, Counselor, please.

Q. You know what? I -- I withdraw the question. Let me ask a different question.

Does the formulation, or -- strike that.

Does the composition of Boschelli

contain 4-[(2,4-dichloro-5-methoxyphenyl) amino] -6-methoxy-7-[-3-(4-methyl-1-pyperazinyl)propoxy]-3-quinolinecarbonitrile? Yes or no?

A. Again, I'm not sure if you got all the brackets right, but we know it's written there. So what I'm trying to say is that the -- this particular compound as such is -- is part of what's in Boschelli Reference Number 31a.

Q. So, yes, the composition of Boschelli includes bosutinib, right?

A. If that's what we're defining bosutinib is, is that chemical formula.

Q. Okay. Can you assume in the question I asked that when I say "bosutinib," I mean the chemical formula? I'm sorry. I thought that was clear. When I say "bosutinib," I mean that chemical formula. Okay? That's what I mean.

MS. PIPER: Objection to form.

Q. Do you understand?

A. Yes.

Q. Okay. Does the composition of Boschelli contain bosutinib?

A. Again, under your definition, this chemical formula, yes.

Q. Okay. And does the composition of Boschelli contain one or more excipients? Yes or no?

A. So, for example -- on page 15 of my report, 53, I talk about excipients as ingredients of a pharmaceutical composition other than the active ingredient. From that standpoint since Boschelli does not contain or -- is likely not to contain pharmaceutical compositions, and all the -- I mean, this is really the whole focus of my report, I would not call those excipients.

Q. Okay. So it is your opinion that the composition of Boschelli does not include any excipients, right?

A. Well, again, there's no indication that what's included are pharmaceutically acceptable. Certainly TWEEN, dextrose, and water can be excipients, and they're in the Handbook of Pharmaceutical Excipients. And they're likely on the GRAS list, as we discussed earlier.

But if we're defining as I do here that they have to be in a pharmaceutical

composition for -- and this is just a summary statement for all the reasons which I discuss here, then they're not excipients as such because it's not likely to be a pharmaceutical composition.

Maybe if someone were to go back and characterize it, and -- maybe they actually do meet specs but there's no indication that they do, and so there's no indication that they're a pharmaceutical composition, or that they're excipients that are ingredients of a pharmaceutical composition.

Q. Okay. One second.

THE COURT REPORTER: Counsel, when you get to a good moment, I could use a break.

MR. BENSON: Yeah. That's what I was getting at. Let's take a break.

THE VIDEOGRAPHER: The time is 11:59 a.m., and we are going off the record.

(Luncheon recess at 11:59.)

A F T E R N O O N S E S S I O N

(1:00)

BERNHARDT TROUT, Ph.D.

resumed, having been previously duly sworn by a Notary Public, was examined and testified further as follows:

THE VIDEOGRAPHER: The time is 1:00, and we are back on the record.

CONTINUED EXAMINATION BY MR. BENSON:

Q. Welcome back, Dr. Trout.

A. Thank you.

Q. So returning to the claim language, what -- and I know we talked about this earlier in the context of what the term means generally to a person of ordinary skill in the art. But what does a -- what does the term "pharmaceutical" mean to you in the context of the claim at issue here; namely, Claim 1 of the '625 patent?

A. So -- and I think it's important, Counselor, it's -- pharmaceutical composition go together here, and I use the construction that -- as I elaborate in paragraph 29 of my

report that the Court construed. And so pharmaceutical composition is what the Court construed and what's written there, "A pharmaceutically acceptable composition containing the specified compound and one or more excipients.

Q. Well, pharmaceutical is an -- it's an adjective, right? And it's modifying composition?

MS. PIPER: Objection to form.

A. Yes. And I guess it's an adverb as used by the Court's construction.

Q. Okay. So in the context of its use in the claim, just pharmaceutical, I mean, what is your understanding of that -- the adjective? What does it mean?

I mean, adjectives in their own right have meaning, right?

MS. PIPER: Objection to form.

A. Well, I think pharmaceutical composition go together, and my understanding is that that's, you know, a part of a -- a claim. And so if you're asking me about the specific use in this claim, I think it has to go

together.

And I can opine on -- or I can tell you, you know, broadly outside of the context of this claim pharmaceutical by itself. But with -- within the claim, I think it has to go with composition.

Q. Well, but each word has its own meaning, right? I mean, the -- an adjective pharmaceutical has a meaning separate and apart from the noun composition; isn't that correct?

MS. PIPER: Object to form. Objection to form.

A. I mean, obviously to the extent that you're asking me a legal conclusion, I leave that to the lawyers to decide. My understanding is that the way the Court looks at it, they go together. If you mean just broadly grammatically, that's correct, they're two separate words.

Q. And so what does pharmaceutical, the adjective, mean to you? Again, just in your -- in the context of understanding this particular patent, what does that term mean to you "pharmaceutical"?

A. Again, you mean -- by "the context" you mean not what's the word in the claim term but just broadly within the context of the patent? Or --

Q. Right. Based on your reading of the patent, what is your understanding of what pharmaceutical means?

A. Okay. So if -- in the context of the patent, I think it's an adjective that modifies composition. So composition is, you know, some -- let's say, as the Court construes, some mixture of different compounds, and the specifics are there.

And then the pharmaceutical modifying composition means that it's not just any composition. It has to be a pharmaceutical composition. And I discuss -- I mean, really, my whole report is about that one term, and so it's all -- all my opinions relate to, really, that term.

Q. So we can agree that from the Court's construction, composition is just generally the -- a composition that contains the necessary components articulated in the construction

itself, namely bosutinib and one or more excipients, right?

MS. PIPER: Objection to form.

A. Right. I guess the specified compound and one or more excipients in the specified compound is -- is, you know, a chemical term, which we've been discussing, which -- you know, depends on how you want to define it. It's a -- a molecular formula which is related to the, you know, active bosutinib, but abstracted from the actual situation in which it's in, in which there were impurities and there are other aspects to it.

Q. Right. So -- but the -- what I'm getting at is that we -- we have an understanding, or I have an understanding as to what you're -- what you understand composition to mean in the context of the Court's construction; namely, it's a composition containing bosutinib and one or more excipients, right?

So -- correct?

A. Well, again, we have been -- we were discussing this morning what bosutinib means,

and we have to be clear from the context. I mean, there's --

Q. With all due respect, if I have not been clear that when I say "bosutinib," I mean the chemical structure, the compound bosutinib, I apologize, but that's what I mean. I don't mean anything else. If I'm talking about anything other than that, I will let you know. But there is -- here it's a compound. I mean, in the chemical arts, what does a compound mean?

A. In the chemical arts, and I know it can be used differently in -- maybe legal or otherwise, but specifically in chemistry, a compound is a -- let's say a defined set of atoms which are connected through chemical bonds.

Q. Okay. And that is exactly the way I'm using bosutinib here because the composition -- the elements of the composition pursuant to the Court's construction is, it contains a specified compound, which is bosutinib, the compound, as that is used in -- in chemistry and one or more excipients, right?

A. Okay.

Q. Okay. So we're in agreement on that, right? A composition is a -- according to the claim is a composition -- now, again, I understand your opinion about pharmaceutically acceptable, and we'll get to that. But just for clarity, a composition is a composition that contains bosutinib and one or more excipients, right?

A. Again, right, if you're defining bosutinib as this chemical formula. It's --

Q. But what --

A. Sorry. Can I just finish my sentence? Thank you.

Q. Yes.

A. Because -- I mean, that -- but that's a key point of my opinions is that if you're talking about it as an API, or as a potential ingredient that could be pharmaceutically acceptable or not, then it's not just the specific compound with a -- a specific molecular formula. It's abstracted from the real situation of impurity profile and the way it's manufactured and whatnot.

Q. Dr. Trout, I appreciate that you have

opinions and that those -- the opinions relate to that particular topic, but --

MS. PIPER: Objection.

Q. -- what I'm looking to is the Court's construction that said a composition contains the specified compound, right?

And we just went through what is the compound. The compound here is bosutinib. And it's a compound. It's not an API. It's not an aggregate of compounds and a bunch of other garbage that may or may not be present. It's the compound. And that's what I'm talking about, the Court's construction.

The Court's construction of the claim is a composition containing the specified compound, which is bosutinib, right? The chemical entity, the compound, bosutinib, and one or more excipients, right?

MS. PIPER: Objection to form.

Q. I mean, do you need to look at the construction? Because it says "specified compound," and we agree that the specified compound -- I thought that was one of the very first things we did today is we talked about the

specified compound being that chemical structure that is articulated in the claim, and we agreed that that structure was bosutinib, right?

A. Right, in the sense I'm happy to consider this chemical structure that's in Claim 1 to be bosutinib just with a -- you know, make sure that we agree that if we call that bosutinib, that's that chemical structure per se, not another manifestation of that in a particular environment.

Q. Right. But it -- correct me if I'm wrong, but there is the question -- the question you're getting to is whether or not there is an inhibiting amount of CML -- a CML inhibiting amount of the compound, right?

MS. PIPER: Objection.

Q. It's, like, how much bosutinib is in there, and what does it look like, right?

MS. PIPER: Objection. Outside the scope of what Dr. Trout opined on.

Q. That's exactly right. You didn't consider that at all, right? You didn't consider how much bosutinib or -- is -- the claim requires, right?

MS. PIPER: Objection. Outside the scope of what Dr. Trout opined on.

A. And I'm confused because there's multiple questions --

Q. You didn't opine on how much bosutinib has to be in the composition of the claim, right?

MS. PIPER: Objection to form.

A. That's correct. I did not opine on a specific amount in this claim.

Q. So then I just want you to focus on the compound itself, just bosutinib. Because the part of the claim that you did consider and opine upon is pharmaceutical composition, and that part of the claim, that part which is all you've testified -- all your opinion relates to, is that -- a pharmaceutically acceptable composition containing the specified compound, bosutinib, and one or more excipients, right?

A. Yes, again, that's fine for a -- defining bosutinib as the -- the chemical formula --

Q. And we are.

A. -- which is in the claim.

Q. And we are. So a composition, according to the claim -- and then I want to get to your opinion which really relates to pharmaceutically acceptable, correct?

MS. PIPER: Objection to form.

A. My opinion relates to -- I mean, everything that I discuss in my report. And pharmaceutically acceptable is a major part of it, and the specifics of the Boschelli reference is also a major part of it.

Q. Right. We agree that there is a composition in Boschelli, right? I mean, we agreed about that this morning?

A. Yes. We can call them a composition. There are a variety of compositions.

Q. Right. And the compositions contain bosutinib and one or more excipients, right?

A. Again, if you are defining -- I mean, they contain other things potentially in them. Those are the key aspects that we have been focusing on, but my report -- I talk about the impurity profiles and I talk about all kinds of other aspects to -- to what's in there, even though they may not be explicitly stated.

And I talk about all the reasons why there are other things in these -- these non-pharmaceutical compositions, potentially non-pharmaceutical compositions.

Q. Right. It is your opinion that pharmaceutically acceptable excludes any kind of impurities in the composition, right?

A. No, that's not what -- my opinion.

Q. Okay. How much -- how many -- what level of impurities can one have in a pharmaceutical composition?

A. So my understanding as a technical expert is that there's a procedure that one would have to go through to determine and make the case for what's acceptable in a particular situation for a particular, you know, proposed active.

Q. And your opinion relates on the things that a person of ordinary skill in the art has to do to obtain FDA approval to sell a drug, right?

MS. PIPER: Objection to form.

A. No, that's -- that's -- I mean, that's part of it, but I talk a lot about a lot of

aspects. It's not -- it's not so crystalized as such.

Q. Okay. So a pharmaceutical composition does not have to be an FDA approvable composition, correct?

MS. PIPER: Objection to form.

A. Not necessarily. I think it -- I think that -- that certainly if it's FDA approvable -- I'm not sure what that means. If it -- but if it's FDA approved, let's say, then -- then that -- that's certainly one example, but that's not the only example.

Q. Okay. So a pharmaceutical composition pursuant to the claims, in your opinion, does not have to be a composition that would meet the standards of FDA approval for a human drug, right?

MS. PIPER: Objection to form.

A. Yes, that's correct.

Q. Okay.

A. Not necessarily. That's an example of what it could be.

Q. Okay. So does it have to be a pharmaceutical composition that would meet the

standards for administering the composition to an animal, for example?

MS. PIPER: Objection to form.

A. Again, I think that's another example of what could be -- again, given my understanding of the construction of this claim, that would fall under a pharmaceutically acceptable composition.

Q. Right. But the question is, does it have to be a composition that would meet the standards of approval for a composition that could be administered to an animal?

A. I don't -- well, maybe potentially approvable by -- by someone, but that's not -- it's not like a threshold, or a, you know, rock-solid criterion.

Q. Okay. What if it's a -- what if it's a composition that the IACUC approves for the administration to animals in a laboratory context? Would that meet the standard?

A. I'm -- I'm not sure if it would meet the standard. I would have to -- I would have to understand the context and -- and what it was approved to do. And, again, there are different

kinds of animal studies. And -- and we talked about what Boschelli 2001 is. And so it depends what it's approved for.

Q. What is IACUC? Do you know what that stands for?

A. Yeah, it's -- I don't know off the top of my head but it's in Wolff -- it's the Institutional Animal Care and Use Committees -- or Committee, I guess, without the S.

Q. So Institutional Animal Care --

A. And Use Committee.

Q. -- and Use Committees.

A. Committees with plural.

Q. And what is your understanding of what the role of the IACUC is in the context of a research laboratory?

MS. PIPER: Objection. Outside the scope of what Dr. Trout was asked to opine on.

A. I don't have an opinion on that.

Q. Do they have to approve protocols for the administration of compositions to animals?

MS. PIPER: Objection. Outside the scope of what Dr. Trout was asked to opine

on.

A. I don't have an opinion on that.

Q. Do pharmaceutical companies have IACUC -- let me ask that a different way. That's kind of a weird construction.

Do pharmaceutical companies have Institutional Animal Care and Use Committees within their organizations?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. I don't have an opinion on that.

Q. Do pharmaceutical companies employ veterinarians to oversee the care of the animals they may or may not be using in research?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. It's not an opinion that I have.

Q. Okay. All right. So if the composition of -- well, if a composition intended to be administered to laboratory animals for the purpose of gauging its therapeutic potential is approved by the IACUC, would that composition be a pharmaceutically acceptable composition pursuant to the claims of

the '625 patent?

A. In this hypothetical, I think it depends on the details and what it was approved for and the reason behind the approval. I -- it -- the details are important.

Q. So you would have to know more details.

What if -- what if the composition of Boschelli was approved by an Institutional Animal Care and Use Committee? Would that change your opinion about whether or not that composition was a pharmaceutical composition?

MS. PIPER: Objection to form.

A. If there's additional information regarding the Boschelli 2001 reference, I would certainly take that into account. I would have to analyze that information to determine how that affects my opinions.

Q. Okay. So the -- so if, in fact, there were evidence that the IACUC had approved of the composition being administered to the animals in Boschelli, that could impact your opinion as to whether or not that formulation in Boschelli was a pharmaceutical composition, correct?

MS. PIPER: Objection to form.

A. It may or may not. If there's additional information about Boschelli outside of the reference and the other references which I considered, I would take that into account.

Q. All right. So a pharmaceutical composition as the Court has constructed it, as far as whether it's pharmaceutically acceptable, it doesn't rise to the standard of something that would be approvable by the FDA for human use, right? That's your testimony?

MS. PIPER: Objection to form.

A. I think my testimony as I gave it before is that that could be one example, but there are other potential examples.

Q. Right. But the question is a little bit different. I just want to make sure I'm absolutely clear that it is not your opinion that pharmaceutically acceptable means the composition has to be a composition that would be approvable by FDA for human use, right?

MS. PIPER: Objection to form.

A. I'm not sure what it means that something is approvable. I think what you're

asking is if it hypothetically had gone through the FDA approval, that's the only thing that I understand. Because -- and in --

Q. Right. A composition could be a -- a composition according to the claims could be a composition that is being used for research purposes, right?

MS. PIPER: Objection to form.

A. Well, it depends on what kind of research. Broadly speaking, in its -- it's possible.

Q. So if it's being administered to humans for the purposes of researching its therapeutic potential, is it a pharmaceutical composition?

A. Again, one would have to go through the same kind of analysis that I went through in, whatever, 25 or so pages on the Boschelli, you know, given the details of this hypothetical you're posing, to make an opinion upon that.

Q. Okay. So based on that response then is it your opinion that it is possible that a composition being administered to patients in a Phase III clinical trial may not be

pharmaceutically acceptable pursuant to these claims?

MS. PIPER: Objection to form.

A. I mean, look, may, there's always some possibility. I would generally think that a composition that's been approved to go through Phase III trials would be pharmaceutically acceptable. There may be exceptions to that. Again, you're asking a broad hypothetical. But generally, I would expect that that would be pharmaceutically acceptable.

Q. Okay. Pushing that a little bit further, would you assume a composition that has been approved to administer to a human in any clinical context would be pharmaceutically acceptable?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and...

A. Yeah, I didn't give an opinion about clinical broadly, and I'm trying to give examples of what could be pharmaceutically acceptable. Again, the -- the focus on my report was on the Boschelli 2001, and, you know, the analysis that I've done of that reference.

Q. Can you think of any example where there's a composition administered to humans and it would not be pharmaceutically acceptable?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.

A. I don't have an opinion about that per se.

Q. Do you have any opinion about -- strike that.

Do you have any opinion about what a composition administered to a laboratory animal would have to look like in order for it to be considered pharmaceutically acceptable?

A. Yes. I think it would have to meet some of the criteria, or the -- the bulk of the criteria that I've gone through here in this report, which Boschelli doesn't meet any of those criteria I've talked about. I think it would have to meet some of them. And, again, it would depend on the context, what the study was done for, and I would have to analyze those details.

Q. Why does it matter what the study is being done for, in your opinion?

A. Because it matters whether the study is attempting to treat animals or is basically doing a study with hypotheses, for example, about how chemicals work, leading to the destruction of those animals one way or another.

Q. What in the Court's construction leads you to believe that pharmaceutically acceptable composition has to be one that is being administered for the purposes of treating?

A. I did not say that it has to be.

Q. Okay.

A. I said that's a potential, you know, example. But that's not really the threshold. I think the threshold is what I've gone through in this report, and it has to, you know, meet some of the criteria. And I've discussed in particular why Boschelli 2001 doesn't meet any of those criteria.

Q. So a pharmaceutically acceptable composition could be a composition that's being administered to an animal even though it's not being administered solely for the purposes of treating, right?

MS. PIPER: Objection to form. And

outside the scope of Dr. Trout's opinion.

A. I mean, again, pharmaceutically acceptable composition, as I've discussed in my report, would have to meet the criteria that I've discussed.

Q. Okay. Well, let's see here. On page -- on paragraph 63 of your report, you say, "Beyond meeting the specifications for the API and excipients discussed above, a pharmaceutical composition as a whole must meet a variety of specifications," and then you are referencing U.S. Food and Drug Administration Q6A specifications, test procedures, and acceptance criteria for new drug substances and new drug products.

So do -- does a pharmaceutical composition have to meet the specifications for -- that FDA sets forth for a new drug product?

A. First of all, just to -- it continues, what you read, to, colon, "Chemical Substances," the Q6A specifications for those. But, no, I'm not saying that it has to meet Q6A.

Q. Okay.

A. I'm saying that's an example.

Q. Okay. So the specifications for the pharmaceutical composition, as you state it here, is going to be defined by the company producing the pharmaceutical composition and is going to take into account safety and efficacy, right?

A. Yes, that's what I've written.

Q. Okay. So if -- if the Boschelli group decided that the specifications for the composition in Boschelli met what they define to be acceptable for a pharmaceutical composition to administer to the animals, isn't it a pharmaceutical composition, according to your own opinion?

MS. PIPER: Objection to form.

A. No.

Q. You don't deny the compositions of Boschelli were given to the mice, right?

MS. PIPER: Objection to form.

A. They were administered to the mice.

Q. They were in administered --

A. They were administered to the mice.

Q. Administered -- right.

Intraperitoneally, right?

A. Well, also orally.

Q. And they were in multiple times for the single mouse, right?

A. Yes. For -- I mean, the -- there's some details in the different experiments but, yes.

Q. Did they kill the mice by administering the drug?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. The mice were meant to be sacrificed, so they were eventually killed in these --

Q. Was the purpose of the drug -- to administer the drug for the purpose of killing the animal?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. I think that the objective of the Boschelli study was not to kill the mice.

Q. What was the objective of the Boschelli folks in administering the composition containing bosutinib, TWEEN 80, and dextrose?

MS. PIPER: Objection. Outside the

scope of Dr. Trout's opinion and report.
A. I didn't speak in my report about the specific objective, so I didn't express an opinion about that.
Q. Okay. Right. So you don't know whether they -- you don't have an opinion as to whether or not they were administering the composition for the purposes of assessing the composition's potential to inhibit CML tumor growth, right?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.
A. Are you quoting from somewhere? Because I --
Q. No. I was just asking a question.
A. Okay. Could you repeat the question, please?
Q. You don't have an opinion as to whether the Boschelli scientists were administering the composition described in that reference for the purposes of assessing the composition's potential to inhibit tumor growth, right?
MS. PIPER: Objection. Outside the

scope of Dr. Trout's opinion and report.
A. That's correct. I've not expressed an opinion about that. I do not have an opinion on that.
Q. Okay. Do you have an opinion as to whether -- strike that.
And you also don't have an opinion as to whether or not the composition was, in fact, capable of inhibiting tumor growth in the mice, right?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.
A. That's right. I did not express an opinion about that.
Q. Okay. Okay. If you could -- you have your report in front of you there?
A. Yes.
Q. Okay. I'm just going to -- I have some questions about some of the language in your report.
Well, before I do that, could I take you to Exhibit D in your binder, please.
A. Okay.
Q. I'm sorry. Exhibit DD.

A. Ah.
Q. Two Ds.
A. Okay. I'm there.
Q. Do you recognize this document?
A. Yes.
Q. And what is this document?
A. This is a -- FDA Guidance for Industry INDs for Phase II and Phase III Studies: Chemistry, Manufacturing, and Controls Information.
Q. Okay. What are Phase II studies?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.
A. And you mean just in general, or in the context of --
Q. In the --
A. -- my report in the case?
Q. Sure. In the context of this particular document, what is your understanding of what a Phase II study would be?
A. So a Phase II study is part of the clinical studies that -- that can be performed.
Q. In -- in humans, correct?
A. Yes. In -- with this -- with respect

to this document, it's for humans.
Q. Okay. And Phase III studies, what is your understanding of what a Phase III study would be, as that term is used in this document?
A. A Phase III study is another phase of clinical studies used for pharmaceuticals.
Q. Okay. All right. And just for clarity then, it is not your opinion that a pharmaceutically acceptable composition has to be a composition that satisfies the requirements of FDA for use in Phase II studies, right?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.
A. I didn't speak, I think, specifically about that, but this is an example, on the other hand, of -- of a composition that could meet the criterion of pharmaceutically acceptable composition.
Q. Okay. But it is possible that a pharmaceutically acceptable composition could be one that does not meet the requirements for use in a Phase II study with humans, right?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.

A. I think my opinion was only about an example of what could -- in this context what could fall under pharmaceutical -- pharmaceutically acceptable excipient.

Q. Pharmaceutically acceptable excipient --

A. Pharmaceutically acceptable composition. Thank you.

Q. So your opinion was, it was limited -- so if I understand you correctly, your opinion was essentially to establish a pharmaceutical composition that you have confidence would meet the standard of pharmaceutically acceptable as that term is used in the patent?

MS. PIPER: Objection to form.

A. No, I wouldn't say it exactly that way. No.

Q. Okay. How did I get that wrong?

A. So my opinions in this report discuss the kind of issues that the person of ordinary skill in the art would -- would think about and engage in in analyzing whether a particular reference, Boschelli 2001 specifically, discloses pharmaceutically acceptable

compositions or not. So that was really what my report was about.

Q. And your opinion about that is that, A, you don't know whether the -- the API used in that composition was sufficiently pure to meet the standard of pharmaceutically acceptable, right?

MS. PIPER: Objection to form.

A. I don't know if I would summarize it so cursorily. I have many pages on this. I mean, for example, in paragraph 69 it says, "As explained in more detail below," but it's kind of a summary statement on one aspect, "the chemical synthesis disclosed in Boschelli 2001 was not designed to lead to and likely not would have led to a pharmaceutically acceptable API."

So I don't know if I would summarize it just in a sentence as you did.

Q. Okay. So -- well, that was one of the things that I wanted to ask you about.

So you say it would not -- would -- likely would not have led to a pharmaceutically acceptable API. So you don't -- you don't foreclose the possibility that it was, in fact,

a pharmaceutically acceptable API that was used in the composition of Boschelli, correct?

MS. PIPER: Objection to form.

A. It's -- you know, it's possible. What I say -- that's why I wrote here, it -- it was not designed to and likely would not have led to a pharmaceutically acceptable API. In other words, I didn't say it's absolutely certainly did not -- likely would not have led to and was not designed to lead to.

Q. So what gave you the opinion that it was not designed to lead to a pharmaceutically acceptable API?

A. Well, I expressed that in multiple pages, from my experience in pharmaceutical manufacturing research and with pharmaceutical manufacturing, and from the references that -- that I've included here in multiple paragraphs in this report, what's disclosed in Boschelli 2001 do not -- were not designed and -- to lead to and likely would have not led to a pharmaceutically acceptable API. So those are the categories of bases for that opinion.

Q. Yeah, it's interesting, I mean, you

don't -- well, I guess you don't have an opinion as to what their intention was with respect to this composition. But certainly they say in the Boschelli reference that their purpose was to administer the composition to animals to gauge the potential of the API to inhibit tumor growth, right? That's what they say?

MS. PIPER: Objection to form. Objection that this is outside the scope of Dr. Trout's opinion and report.

A. As you said, I don't have an opinion on that particular subject.

Q. Okay. So one thing you do -- an opinion you give regarding the API is that when creating a pharmaceutically acceptive active appropriate particle size and type, pressure, column length, and flow rate must all be taken into account.

Right? You say that at paragraph 71?

MS. PIPER: Objection to form.

A. Right. I think that you substantially read what I say at the bottom of page 22 in the middle of paragraph 71, and it has to be understood in the context of the paragraph in

the section, too, but that's I think substantially what's written there.

Q. So is it your opinion a pharmaceutically acceptable active is one wherein the particle size of the active is known?

A. I don't have an opinion about that. I wanted to emphasize this appropriate -- I think -- this appropriate particle size we're talking about within the context of column chromatography, I'm talking about the particles in the chromatographic equipment.

Q. Okay. What, if anything, do you know about the particle size and type in the column chromatography apparatus used in Boschelli?

A. Well, Boschelli, for example, on page 3974, on the right column, the last full example, which references 31a, and I think I quote it in my report, too, but it says, "The residue is purified by column chromatography," and the sentence continues.

And so Boschelli doesn't disclose that, and these are the kind of things that one would expect to be disclosed if one were to make

a pharmaceutically acceptable composition.

Q. But what they say is that the residue is purified by column chromatography, right?

MS. PIPER: Objection to form.

Q. I mean, isn't that what they say, purified?

MS. PIPER: Objection to form.

A. I mean, that's what's written there, and I discuss this in my report.

Q. You don't believe them?

MS. PIPER: Object to form. And outside the scope of Dr. Trout's opinion.

A. I'm -- I don't -- I -- I see what's written there, and I -- I certainly believe them. I think the important thing is to understand the context of this purification. And I -- you know, I discuss this in multiple paragraphs, and I -- around paragraph 71 that we discussed, and before that in paragraph 70, and -- and beyond.

But I think it's important, in answering your question, in paragraph 70, I start out, "A POSA reading Boschelli 2001 would conclude that Compound 31a was synthesized

without much attention paid to purification or to any of the specifications required for active compounds that are to be included in a pharmaceutical composition," and I go on.

So they purified it for a certain purpose, but not for the purpose of creating a pharmaceutical composition based on their disclosure.

Q. Okay. They don't say that, right? They don't say, we purified it -- strike that.

Boschelli doesn't say they made a crude purification of bosutinib, right?

A. Correct. So I mean, citing that, those are not the words that they use.

Q. Okay. Now, let me ask you a different question. Let's say for the sake of argument that it wasn't purified to the standards that would be required for a pharmaceutically acceptable active. At the time of the invention here, would a person of ordinary skill in the art have been able to synthesize bosutinib and purify it to a standard that would be -- would render it acceptable for use in a pharmaceutically acceptable composition?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.

A. I haven't done that analysis, and I don't have an opinion on that.

Q. Okay. Let's say for the sake of argument the TWEEN 80 used in the composition of Boschelli was not pharmaceutical grade TWEEN 80, at the time of the invention would a person of ordinary skill in the art have been able to formulate a composition that included pharmaceutical grade TWEEN 80?

MS. PIPER: Objection. Outside of the scope of Dr. Trout's opinion and report.

A. I didn't express an opinion on that issue.

Q. Okay. Then let me ask you this question. At the time of the invention, could a person of ordinary skill in the art have reproduced the composition of Boschelli in such a way that it would meet the standard of a pharmaceutically acceptable compound or composition as you understand that claim to require?

MS. PIPER: Objection. Outside the

scope of Dr. Trout's opinion and report.
A. I don't have an opinion on that.
Q. Okay. What are the pH requirements for a suspension being administered ip?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.
A. I didn't express a -- such opinions. I don't have an opinion on that.
Q. Are you aware of any pharmaceutically acceptable compositions with a pH of approximately 5.9 that have been administered to animals ip?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.
A. To the extent that you're not talking about my paragraph 77, I don't have an opinion on it. I mean, the pH 5.9 is in my paragraph 77.
Q. So this is something -- again, in -- sticking to paragraph 77, you say, "Were the Boschelli composition intended to be a pharmaceutical composition, potential issues such as choosing a desired pH and maintaining it would have likely been addressed."

MS. PIPER: Objection to form.
Q. And my question to you is, it likely would have been addressed but is it your opinion that it's not necessary in all circumstances for such things to be addressed?
A. Right. That's why I say "likely." I'm not saying it's absolutely necessary. I say that it's likely. And, again, this is one part of the totality of the evidence which led me to my conclusion.
Q. Okay. So is it possible that it wasn't necessary for pH adjustment to be addressed in the composition of Boschelli?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
A. Frankly, I don't understand the question. But to the extent that I do, I think it's outside of my scope of my opinions.
Q. To make sure that I understand, let me rephrase the question. Can you envision a scenario wherein it would not have been necessary for the investigators in Boschelli to adjust the pH of the composition they use to administer to the mice?

A. I don't think I talk about adjustment of pH. But I'm -- maybe if you could -- we're still talking about paragraph 77?
Q. Uh-huh.
A. Again, my opinion is, potential issues such as choosing a desired pH and maintaining it would have likely been addressed, even reporting it potentially. So that's what my opinion is about.
Q. Okay. At the time of the invention would persons of ordinary skill in the art know how to choose and maintain the pH level for a pharmaceutical composition?
A. I mean, I -- I think it depends on the details. My point here -- in general, it might or might not. My point here is that it -- it doesn't even seem to be in the minds of the authors of the paper, and it's something that would have been -- would have come to mind potentially or likely have been addressed.
Q. What is tonicity?
A. And I think you're referring, just to clarify, to my paragraph 79?
Q. Just generally. But, yes, you do use

that term in paragraph 79.
A. Okay. So just -- not -- I'm sorry. I'm confused.
Q. I'm just asking, what is your understanding of the term "tonicity"? What does that mean?
A. Outside of the scope of my report but just generally?
Q. I mean, specifically as you use it in your report. You use the term, so I just want to understand what it means to you.
A. Okay. What it means is a -- a particular, let's say, concentration of -- of, let's say, a -- an aqueous solution, the different concentration of the solutes in that solution leading to a value tonicity usually measured in particular units like milliosmoles, which is a measure of how -- how much solutes, I'll say it that way, are in the solution, concentration of such.
MR. BENSON: Okay. Why don't we take -- I think I'm almost finished. Why don't we take a short break, and I'll just confer with my colleagues here. And we'll

come back and finish up. Okay?
THE WITNESS: Okay.
THE VIDEOGRAPHER: The time is 1:58 p.m., and we are going off the record.
(Recess from 1:58 to 2:14.)
THE VIDEOGRAPHER: The time is 2:14 p.m., and we are back on the record.
Q. Okay. Just a few more questions.
The patent in -- at issue here, the '625 patent, also describes xenograftic studies using bosutinib with mice, correct?
I'll direct you to, for example, Column 13.
A. Yes. I see that, Column 13 and 14, yes.
Q. Okay. So it says that the -- "The compounds of formula 1 ('the compounds'), originally identified as a Src inhibitor, are shown here to be a potent anti-proliferative and proapoptotic agent against CML cells in culture."
Right? Did I read that correctly?
A. Yes, that's what's written there. Yes.

Q. And then next it says, "The apoptotic activity of the compounds against CML cells in culture is mirrored by its activity in vivo against CML xenografts."
Right?
A. Yes, that's what's written.
Q. And it says, "The K562 tumors regress in nude mice when the compounds are administered p.o. once a day."
Right?
A. Yeah, I mean, just -- since you're quoting didn't say "the" but, yeah, substantially that's right.
Q. What does p.o. stand for? Do you know?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
A. I -- I guess it's outside of my opinion.
Q. Okay. I didn't really ask your opinion. I just asked if you knew. You can answer.
A. Yes, I know.
Q. Okay. What does it mean?

A. I think it means oral administration.
Q. Thank you.
Now, let's go over to Column 14. It says here -- now, this is describing the nude mice data with the CML cell xenografts, correct?
Beginning at about, looks like line 3?
MS. PIPER: Objection. Outside of the scope of Dr. Trout's opinion and report.
A. Yeah, I don't have an opinion on what kind of cells those were.
Q. Okay. All right. Well, that's fine.
It says here that -- the very last sentence says, "The compound of Example 1 was administered p.o. in 0.4 percent methocel/0.5 percent TWEEN at 75 mg/kilogram once a day for 5 days (8 mice/group)."
Did I read that correctly?
A. Yes.
Q. Do you know what methocel is?
A. Yes.
Q. What is it?
A. It's a -- an abbreviation for methylcellulose.
Q. Okay.

A. Or maybe not an abbrev -- a shortened version of methylcellulose.
Q. And would this -- the .4 percent methocel/.5 percent TWEEN, is this a -- is there also water in this composition, as far as you can understand?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.
A. I didn't analyze it as such.
Q. Would you expect, based on the description here, that there's also water in this composition?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.
A. I didn't offer an opinion about what else is in the -- in this compound of Example 1, and -- and the other things.
Q. Well, let me ask you this. This composition that's described here in Column 14, is that a pharmaceutically acceptable composition?
MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.
A. I don't have an opinion about whether

that's pharmaceutically acceptable or not.

Q. What would you need to know to make that determination?

A. Well, I would need to do a similar kind of analysis as to what's in my report, the analysis that I did for the Boschelli 2001.

MR. BENSON: Okay. I don't think I have any further questions for you, Dr. Trout. Thank you very much for your time.

THE WITNESS: You're welcome.

THE VIDEOGRAPHER: Is that it?

MR. BENSON: Before we go off the record, do we -- let's designate -- we'll designate this as confidential. I don't think there's anything but we'll just go through it and double-check, but for the time being we'll just designate it as confidential.

(Continued on following page to include jurat.)

THE VIDEOGRAPHER: The time is 2:20 p.m., and this ends the deposition of Bernhardt Trout.

(Time noted: 2:20 p.m.)

BERNHARDT TROUT, Ph.D.

Subscribed and sworn to before me this day of 2019.

C E R T I F I C A T E

STATE OF NEW YORK)
) Ss.:
COUNTY OF NEW YORK)

I JEFFREY BENZ, a Certified Realtime Reporter, Registered Merit Reporter and Notary Public within and for the State of New York, do hereby certify:

That BERNHARDT TROUT, Ph.D., the witness whose examination is hereinbefore set forth, was duly sworn by me and that this transcript of such examination is a true record of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage; and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 14th of August, 2019.

JEFFREY BENZ, CRR, RMR

----------INDEX----------

----------EXHIBITS----------

ERRATA SHEET FOR THE TRANSCRIPT OF:
Case Name: Wyeth LLC v. Alembic Pharmaceuticals
Dep. Date: August 7, 2019
Deponent: Bernhardt Trout, Ph.D.

Pg. Ln.	Now Reads	Should Read	Reason
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Signature of Deponent

SUBSCRIBED AND SWORN BEFORE ME
THIS ____ DAY OF _____, 2019.

_____

(Notary Public) MY COMMISSION EXPIRES: _____

Exhibit C

Frequently Asked Questions About the Public Health Service *Policy on Humane Care and Use of Laboratory Animals*

Axel Wolff, MS, DVM, Nelson Garnett, DVM, Stephen Potkay, VMD, Carol Wigglesworth, Denis Doyle, MA, and Venita Thornton, DVM, MPH

The authors answer eight questions commonly asked of the Office of Laboratory Animal Welfare concerning the Public Health Service *Policy on Humane Care and Use of Laboratory Animals*.

The authors are affiliated with the Office of Laboratory Animal Welfare, National Institutes of Health. Please send reprint requests to Wolff at OLAW, NIH, RKL1, Suite 360, MSC 7982 6705 Rockledge Dr., Bethesda, MD 20892.

The Office of Laboratory Animal Welfare (OLAW) of the National Institutes of Health (NIH) develops, implements, and oversees compliance with the US Public Health Service (PHS) *Policy on Humane Care and Use of Laboratory Animals*[1] (*Policy*). The PHS *Policy* and the US Department of Agriculture's (USDA's) Animal Welfare Regulations[2] are the two principal federal documents that set forth requirements for animal care and use by institutions using animals in research, testing, and education. One of OLAW's primary functions is to assist institutions in implementing PHS *Policy* by responding to policy-related questions. This is accomplished by collaborating with organizations and individuals in preparing guidance for Institutional Animal Care and Use Committees (IACUCs)[3–5], supporting the publication of monographs on various aspects of animal care and use programs[6,7], and publishing *Policy* interpretations in articles[8–18] and other formats[19–30]. OLAW also sponsors seminars and training that specifically address current topics covering animal care and use, and issues guidance notices in the NIH Guide for Grants and Contracts (formerly as "Dear Colleague" letters), all of which are found on the OLAW website (http://grants.nih.gov/grants/olaw/olaw.htm). The following represent several additional questions frequently asked by institutions and the OLAW responses.

1. Does the IACUC need to require that the investigator submit the grant application, or portions thereof, along with the IACUC animal use protocol form for review by the IACUC? Is the IACUC required to compare the two for consistency?

PHS *Policy* (IV.D.) requires the institution to verify, before award, that the IACUC has reviewed and approved those components of grant applications and contract proposals related to the care and use of animals. This position is reiterated in NIH Grants Policy Statement under Part II, Terms and Conditions. Most institutions have developed an IACUC protocol form and require investigators to provide detailed information about the proposed use of the animals on this form. The signature of the authorized institutional official on any PHS application or proposal indicates the organization's commitment to comply with the laws, regulations, and policies to which an activity is subject. Institutional submission of IACUC approval, subsequent to submission of the application/proposal, must represent approval of the information originally submitted in the application/proposal, or include notification of any significant changes required by the IACUC.

Although there is no explicit requirement for the IACUC to do a side-by-side comparison of the application/proposal and the IACUC protocol review form, it is an institutional responsibility to ensure that the information the IACUC reviews and approves is consistent with that contained in the application/proposal to be funded. Institutions are free to devise a workable mechanism to accomplish this end. One excellent way to prevent problems of inconsistencies between the information submitted to the PHS and that on the IACUC protocol review form is to implement a procedure for direct compar-

ison[23]. If a procedure of direct comparison is adopted, the individual(s) charged with conducting the comparison should be appropriately qualified to identify inconsistencies. Some institutions have delegated this responsibility to a particular office or position (*e.g.*, sponsored programs office, compliance office); others have asked Departmental Chairs to verify consistency[31].

2. Our IACUC has several categories for the approval of animal study protocols. Which one to use depends on the kinds of issues it identifies during review. We are sometimes unsure how best to characterize the approval status of these projects. Can OLAW provide any advice as to what constitutes appropriate terminology for approval of a protocol?

The PHS *Policy* recognizes only three outcomes of IACUC reviews of proposed activities (protocols) related to animal care and use, as well as proposals for significant changes in previously approved ongoing activities. They are 'approve', 'withhold approval', and 'require modifications to secure approval'. OLAW is aware that some institutions have chosen to use different words and phrases to characterize the latter of these outcomes, such as 'conditionally approved', 'approval pending', 'provisionally approved', 'approved with stipulations', 'administrative approval', and 'limited approval'. We should note that several incidents of suspensions and noncompliance are reported by institutions to OLAW each year that are related to the conduct of unauthorized animal studies by investigators who have misinterpreted IACUC responses or the approval categorization of their proposals. To avoid such misunderstandings and the subsequent necessities to take corrective actions and report to OLAW, this Office recommends that IACUCs use language that is as unambiguous as possible in communicating the results of their reviews of animal study protocols. We suggest that institutions can do this by adhering to the language of the *Policy* and avoiding use of the words 'approved' and 'approval' to describe the outcome of any review that is not an unequivocal approval and making it known that no animal work may commence without an unequivocal approval. In addition, the IACUC approval date submitted to PHS agencies as part of a grant application or contract proposal must reflect the date of final approval.

3. Are the scientists at our institution allowed to use non-pharmaceutical-grade chemical compounds in physiological preparations involving laboratory animals? Please clarify whether this is an allowable practice and whether it makes a difference if the compounds are used in survival versus nonsurvival experiments.

The use of non-pharmaceutical-grade chemical compounds in experimental animals under certain circumstances has been, and will continue to be, a necessary and acceptable component of biomedical research. OLAW and the USDA have determined that their use should be based on (1) scientific necessity, (2) nonavailability of an acceptable veterinary or human pharmaceutical-grade compound, and (3) specific review and approval by the IACUC[32]. In preparing and reviewing proposals to use non-pharmaceutical-grade products, investigators and IACUCs should consider a number of related animal welfare and scientific issues including safety, efficacy, and the inadvertent introduction of research-complicating variables. Although one can assume that issues such as sterility, pyrogenicity, stability, pharmacokinetics, and quality control have been addressed during the course of producing pharmaceutical-grade drugs, one cannot say the same for substances produced in the research laboratory using non-pharmaceutical-grade chemical compounds. Cost savings alone do not adequately justify the use of non-pharmaceutical-grade compounds in animals. Although the potential animal welfare consequences of complications are less evident in nonsurvival studies, the scientific issues remain the same. The principles and need for professional judgment just outlined still apply.

4. Because of time constraints and the needs of our investigators, our IACUC reviews some protocols by sending each member a copy and then polling them to determine whether they approve. Is this procedure in compliance with the PHS *Policy* if the IACUC members, at a subsequent full-Committee meeting, are asked to reaffirm their votes? Is this procedure appropriate, and if not, what must we do to correct the situation?

No. The initial polling of members is not sufficient for approval and initiation of work on animals. Only full Committees or designated members can approve animal study protocols, in accordance with the PHS *Policy* (IV.C.2). IACUC members may use electronic or other forms of polling to call for a full-Committee review, but not to vote[12,17]. Any animal studies undertaken on the basis of approvals resulting from such polling would not be compliant with the PHS *Policy*. Recognizing that urgency may sometimes be an issue in considering animal study protocols, the PHS *Policy* allows for designated review by at least one qualified member, appointed by the IACUC Chair, provided that all other voting members have had an opportunity to request full review and that no member requests a full-Committee review.

5. Several investigators at our institution wish to use surgically modified anmals in their research but do not want to perform the surgery in-house. We are considering the purchase of such animals and would like to know whether the PHS *Policy* applies to customized surgery peformed at vendor facilities.

The PHS *Policy* is applicable to all PHS-supported activities involving animals, whether the activities are performed at a PHS agency, an awardee institution, or other institution (PHS *Policy* at I., II., III., and V.B.). OLAW has provided guidance regarding animal use (antibody production) that takes place outside the applicant/assured institution through subgranting or subcontracting[33]. That guidance may also serve as a template for determining whether other activities such as

customized surgery are covered by the PHS *Policy*. In this regard, and with respect to applicability of the PHS *Policy*, a determining issue is whether the surgery is conducted in response to a specific custom request or whether the animals were previously modified and available before the request was made. If an investigator requests that a specific custom surgical procedure or procedures be performed on an animal for use in activities funded by the PHS, then the organization that conducts the procedure(s) is considered a performance site and must either have on file with OLAW an approved Animal Welfare Assurance or be included as a component of the applicant organization's Assurance.

6. We are a small antibody producer using rabbits, mice, and goats, and our work supports numerous clients, including some funded by the PHS. When we applied for an Assurance, OLAW informed us that we could not approve one 'blanket protocol' to cover all of our antibody production procedures, even though the work is essentially always the same. Please clarify.

Provisions of the PHS *Policy* apply to all Assured institutions regardless of their size or mission. They include the requirement for the IACUC to "review and approve, require modifications in (to secure approval) or withhold approval of those components of PHS-conducted or supported activities related to the care and use of animals," (PHS *Policy* at IV.B.6.) on a project-specific basis. Consequently, each proposed protocol involving antibody production as well as significant changes (e.g., amendments) to previously approved protocols must be submitted for IACUC review and approval, taking into account the aims of the study and the methods proposed to avoid or minimize pain or distress to the animals (PHS *Policy* at IV.C.1.). For example, reviews of proposed ascites monoclonal antibody production in mice must also critically address alternative (*in vitro*) methods as well as pain and distress issues[6,33]. Another example would be a request for a custom antibody against a specific protein for the purpose of vaccine development, followed by a request for an antibody against a different protein to be used for the same purpose. In both instances, *Policy* would require either an amendment or a new protocol. As is the case with any new protocol or proposed significant change to a previously approved protocol, the PHS *Policy* allows for either full-Committee or designated-member review. OLAW recognizes that many aspects of antibody production are routine and recommends that institutional Standard Operating Procedures (SOPs) be developed that describe species-specific techniques for immunization, titer determinations, volume blood collection, and associated procedures. One may cite IACUC-approved SOPs in proposed project-specific protocols or proposed amendments to avoid needless repetition. Under these circumstances, it is possible to combine multiple projects, or even multiple investigators, under a single protocol. However, for PHS *Policy* purposes, IACUC approval of each project-specific protocol submission or amendment must be readily identifiable and amenable to tracking.

7. May a former employee or former student of our institution be considered for appointment to our IACUC as a nonaffiliated member?

PHS *Policy* (IV.A.3.b.4.) defines the nonaffiliated member as an "individual who is not affiliated with the institution in any way other than as a member of the IACUC, and is not a member of the immediate family of a person who is affiliated with the institution," and the USDA's Animal Welfare Regulations expect the individual to "provide representation for the general community interest[34]." The *Guide*[3], which calls this person the "public member," requires additionally that the individual not be a current laboratory animal user. Regarding the service of a former employee in the capacity of a nonaffiliated member, the appointing official would have to receive assurance that the person is not in any way conflicted or beholden to the institution[35]. If there are no discernable ties or ongoing affiliation with the institution, then it would be permissible to consider appointment of the former employee or former student to the IACUC. It is important for officials who appoint IACUC members to determine whether real or perceived conflicts of interest exist and make the appropriate choices to avoid criticism about the institution's or the Committee's integrity. Choosing an individual who is unambiguously 'nonaffiliated' is the best way to fulfill the letter and the spirit of this provision.

8. Our IACUC has encountered a problem with investigators who do not submit their protocols for review in time to gain approval before the three-year expiration date. Is it permissible to grant an administrative extension of IACUC approval so as to avoid expiration?

No. For PHS purposes, IACUC review following the provisions at IV.C.2. of the PHS *Policy* must be accomplished at least once every three years[1]. The IACUC may not extend the three-year approval by any means other than IACUC review and approval using the procedures of IV.C.2. When IACUC approval expires, it is no longer valid. Continuation of animal activities beyond the expiration is a serious and reportable violation of PHS *Policy*.

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